that there was probably no substance present specific for dust

Storm van Leeuven,[4] in developing his theory of climate or "miasma" as a factor in asthma, reports experiments in which grain infected with *Aspergillus fumigatus* or with *Penicillium* produced anaphylactic symptoms or even death in guinea-pigs exposed to it at times after the first exposure He also observed that penicillia and aspergilli were absent from the air in the localities in which asthmatic persons were free from attacks He suggests that the influence of locality may be due to the bacteria yeasts and molds growing there but attributes the attacks of asthma to substances produced by these saprophytes rather than to the organisms themselves

The first definite proof of the causation of asthma by fungous spores was apparently brought by Cadham[5] In 1924 he reported three cases in workers in wheat fields due to the spores of the wheat rust (*Puccinia graminis*) The spores gave a positive skin reaction in these cases and 'a whiff of a few rust spores was sufficient to induce a paroxysm"

In 1928, Hansen[6] reported a number of cases in which asthma could be incited by spores of molds which he cultivated from the surroundings of the patients, who also gave skin reactions to extracts of the fungi The species to which he found patients sensitized were *Aspergillus fumigatus Aspergillus glaucus* or *Aspergillus nidulans*, and *Penicillium "glaucum"* He describes, however, a patient who had asthma whenever a certain cat entered the room He cultivated *Aspergillus niger* from the cat s fur and the patient gave a strong skin reaction to an extract of its spores

REPORT OF CASE

A man aged 37 had been subject to frequent attacks of asthma, which began following a severe bronchitis in childhood For the past twelve years he had had also a persistent eczema of the hands and feet which had recently involved the lower leg His father was a leather dealer He remembered that in his boyhood contact with hides brought on asthmatic attacks He had always associated these attacks with the smell of musty but not putrid animal material The patient was a mechanical engineer and he had noticed that when his machinery was cleaned he had no trouble if washed rags were used but was apt to have an attack if the cleaners used unwashed rags He had also had attacks on entering old damp houses or antique shops and associated these attacks with the smell of musty carpets He had been often able to predict that he would have an attack in a certain room or house by the smell when he entered He invariably had an attack on entering a stable or a menagerie, but contact with horses in the open did not cause symptoms

His attacks of eczema and asthma had not always coincided On his return to a house where he had had severe attacks of asthma the eczema also flared up, but on his moving to another house the asthma was relieved but the eczema was uninfluenced Repeated examinations of the skin from the lesions between his toes and on his hands had not shown pathogenic fungi On three occasions however cultures from a patch of eczema on his ankle gave a growth of *Aspergillus nidulans*

During a sea voyage both the asthma and the eczema cleared up entirely

The patient s condition had been thoroughly studied previously from the point of view of sensitization Intradermal tests showed a definite reaction to several foods abstinence from which was tried without influencing the attacks Intradermal tests were positive also to tobacco insect powder orris horse epidermis and dust He reacted to an extract of dust from an office where he worked Attacks of
occur after the use of tobacco or orris or
horses

The history otherwise was irrelevant An
eczema the patient s grandmother had asth
examination did not reveal anything of signific

At the time our observations were begun th
returned to the old family house in the suburbs
he was always subject to attacks On going i
cellar to remove some trunks he had a very seve
few weeks later on unpacking these trunks in a
ment where he had been free from asthma he
similar attack

Knowing that he was sensitive to dust and e
dust in places where molds grew we exposed
Sabouraud agar in this cellar Four species of
recovered and intradermal tests were made with
suspensions of the cultures He gave a strong r
one of these *Alternaria* 1305 certain species of whi
cause well known plant diseases among them the early
potato (*Alternaria solani*) Ginseng blight (*Alternari*
and apple leaf-spot disease (*Alternaria mali*) Othe
grow saprophytically on decaying organic material a
spores occur in dust along with those of the commo

TABLE 1 —*Intradermal Reactions*

Fungus	Source	Preparation	Nitrogen per 100 C c or Dilution	I
Alternaria 1305	Cellar	Carbon dioxide extract	N = 0 25 mg	Po
Alternaria 1305	Cellar	Filtered broth	1 = 10 000	Po
Alternaria 1305	Cellar	Spore suspension		Pos
Pachybasium (species)	Cellar	Spore suspension		Dou
Spicaria (species?)	Cellar	Spore suspension		Dout
Penicillium (species)	Cellar	Spore suspension		Doub
Penicillium 1219	Cellar	Carbon dioxide extract	N = 25 mg	Positi
Paecilomyces varioti	Room	Carbon dioxide extract	N = 1 mg	Positi
Paecilomyces varioti	Room	Carbon dioxide extract		Positiv
Penicillium 1220	Room	Carbon dioxide extract	N = 1 mg	Positive
Trichoderma köningi	Room	Carbon dioxide extract	N = 1 mg	Doubtfu
Circinella spinosa 1462	Room	Carbon dioxide extract	N = 60 mg	Negative
Aspergillus nidulans	Lesion on leg	Carbon dioxide extract	N = 0 7 mg	Positive
Cephalothecium roseum	Stock	Carbon dioxide extract	N = 0 8 mg	Positive
Aspergillus niger	Stock	Carbon dioxide extract	N = 25 mg	Negative

The patient was then caused to inhale a powder prepared by drying and grinding the washed felt from an old broth culture of *Alternaria* 1305 This incited a typical paroxysm of asthma which required relief by ephedrine and which recurred at intervals for twenty-four hours

This seemed to prove that some of the attacks of asthma were due to sensitization to this fungus It remained to be shown whether other molds had a similar effect and it seemed of interest to determine what type preparation was most satisfactory for testing Intradermal tests with the culture mediums used were negative but in order further to exclude this factor extracts were made by taking the felt from the old cultures on maltose broth washing it placing it in a mortar with carbon dioxide snow and sand and grinding the frozen fungus to a fine powder This powder was then extracted by adding a fluid containing 1 per cent normal sodium hydroxide 0 9 per cent sodium chloride and 0 5 per cent phenol (carbolic acid) and heating to 56 C for one hour The extracts were filtered through Berkefeld candles and tested for sterility Their nitrogen content was determined by a micro-Kjeldahl method The results of some of our numerous experiments are summarized in table 1

Table 1 shows the results of intradermal tests with fungi isolated from the cellar and the room where the patient had attacks with a strain isolated from his eczematous lesions and with two stock strains

The extracts of *Alternaria Cephalothecium* and *Aspergillus nidulans* were used only in high dilution becau

---

[4] Van Leeuven W S Allergic Diseases Philadelphia J B Lippincott Company 1925 p 58

[5] Cadham F T Asthma Due to Grain Rusts J A M A. **83** 27 (July 5) 1924

[6] Hansen Behandl d deutsch Gesellsch f inn Med **40** 204 1928

The Journal

OF THE

American Medical Association

EDITED FOR THE ASSOCIATION UNDER THE DIRECTION OF THE BOARD OF TRUSTEES BY

MORRIS FISHBEIN, M D

VOLUME 94 JANUARY—JUNE, 1930

AMERICAN MEDICAL ASSOCIATION CHICAGO 1930

amount of blood lost did not exceed 100 cc The right side of the chest was dull up to the fourth rib anteriorly hyperresonant above this, and tympanitic over the entire right side of the back. The percussion note was normal over the left side of the chest.

Roentgen examination on the following morning showed the heart and the mediastinum greatly displaced to the right (fig 3) In the upper part of the right side of the chest was a definite area of pneumothorax and adhesions posteriorly the air extended from the apex to a fluid level which was at the level of the right fifth rib anteriorly (fig 4) There was a fracture of the right fourth rib in the axillary line. Forty-eight hours after the injury the patient coughed up several blood clots and the next morning there was almost complete return of the heart and the mediastinum to the normal position (fig 5) Examination three months after the accident revealed the heart and mediastinum in normal position and pleural thickening over the site of the fractured rib (fig 6) There were slight evidences of old pulmonary tuberculosis

COMMENT

Patient 1 shows a typical valvular pneumothorax, partially relieved by aspiration but persistent over several months The probabilities are that the right lung will not reexpand In contrast, patient 2 shows a pneumothorax with hemorrhage into the lung Part of this blood was expectorated and the rest clotted, plugging a bronchus Massive collapse followed and was relieved by coughing up the blood clots It is suggested that massive collapse is the explanation of the dulness occasionally found in cases of pneumothorax

ABSTRACT OF DISCUSSION

Dr Kenneth D A Allen, Denver It is rather remarkable that the literature tells us so little about atelectasis as a complication, or as a fundamental part of pneumothorax, for such it surely is Of course, it is very rare indeed to see one case such as Dr Harvey's, which demonstrates roentgenologic signs of both conditions Many pneumothoraces however, undoubtedly have as part of their fundamental pathologic changes a massive collapse of the lung on that side Surely as the air is introduced into the chest, the lung in its contraction gradually occludes larger and larger bronchioles and bronchi The speed of this occlusion process depends somewhat on the amount of moisture in the bronchial tree It appears then that these two conditions, in spite of the fact they have different roentgen signs, exist together We can understand and read our plates in cases of pneumothorax to more advantage if we keep the atelectatic process constantly in mind. The two conditions show diametrically opposed roentgen signs Pneumothorax shows depressed diaphragm, separated ribs the heart displaced to the opposite side, a visible lung margin and increased radiolucency Atelectasis when it exists alone shows a raised diaphragm, no lung margin, compressed ribs decreased radiolucency, and heart displaced to the affected side Yet when there is pneumothorax, the two conditions may exist together with pneumothorax dominating the picture There are however, two roentgen signs which are common to these conditions Under the fluoroscope, the heart moves to the affected side on inspiration in both conditions and both show compensatory emphysema of the opposite lung The symptoms of massive atelectasis are almost identical with those of pneumothorax which has been incurred rapidly—a raised temperature, mild leukocytosis, dyspnea and anxiety—and I wonder whether the untoward symptoms of pneumothorax are not due to atelectasis Perhaps in making an artificial pneumothorax, or removing excess air if we would give more attention to maintaining the bronchial tree free from moisture by bronchoscopy or posture we might get fewer untoward symptoms in the former and the lung would expand better in the latter instance.

Dr C T Burnett, Denver It is not the extent of the pneumothorax but the rapidity of development that determines symptoms We produce occasionally pneumothoraces that are as extensive as this one Ordinarily as in Dr Harvey's first patient, we attempt to avoid this marked mediastinal displacement. West's statistics were published in 1897, prior to the routine use of the roentgen ray and to the frequent demonstration of silent pneumothoraces I believe that his statistics of 70 per cent are far too high Bradford, in 1918 stated that no case had yet been seen in association with pneumothorax or with pleural adhesions and emphasized the importance of this in relation to the theories on etiology As late as 1928 Jacobaeus claimed priority in reporting two cases of massive collapse one in acute pneumonia and one in a patient with profuse pulmonary hemorrhage. He suggests that in pulmonary hemorrhage massive collapse probably occurs with much greater frequency than we have thought The collapse that was noted in this patient occurred sequential to trauma, but it differs from such cases in that definite pulmonary hemorrhage occurred It is much easier to explain on the basis of bronchial plug However there is the trauma and one has to consider the possible reflex effect in producing the massive collapse Regarding Dr Allen's suggestion that massive collapse occurs commonly in pneumothorax I rather question that. We produce pneumothorax in the presence of potential infection in fact, there is always infection when we produce it and it is frequently secondary infection. It seems to me that if when inducing pneumothorax we were also inducing massive collapse, we would not have the excellent results that attend the use of therapeutic pneumothorax

Dr. Joseph L Harvey, Denver We should keep definitely in mind that a compressed lung, a massive collapse and an atelectasis are distinct whether the lung is compressed by air in the pleural cavity or fluid in the pleural cavity Of course, the air is out of the alveoli as well but in massive collapse we have quite a distinct disease, which we should not confuse with a compressed lung

---

RELATION OF VINCENT'S ANGINA TO FUSOSPIROCHETAL DISEASE OF THE LUNGS*

DAVID T SMITH, M D
RAY BROOK N Y

There is considerable evidence in the literature for the belief that the anaerobic organisms present in Vincent's infection of the upper respiratory tract may under certain conditions initiate a severe or even fatal pulmonary infection Though the lesions in the lungs and bronchi generally occur as a complication of Vincent's angina, they are occasionally primary These cases of fusospirochetal disease are usually sporadic but at times the infection may definitely be traced from patient to patient In this paper I give a brief summary of the reports in the literature and place on record three additional cases observed at the New York State Hospital for Incipient Tuberculosis in which fusospirochetal disease of the lungs followed exposure to cases of Vincent's infection of the upper respiratory passages

Bruce[1] reported a case of primary Vincent's infection of the larynx and trachea with secondary extension into the tissues of the neck and into the lungs which resulted in death on the eleventh day after the onset At necropsy, fusospirochetal organisms were recovered from all the lesions Arrowsmith[2] observed a case in which the primary infection was in the larynx with subsequent extension to the lungs The swelling of the larynx embarrassed the respiration to such a degree that a tracheotomy was performed Pus from the trachea and sputum from the lungs contained Vincent's organism in practically pure culture Gomez[3] saw a

---

* From the New York State Hospital for Incipient Tuberculosis

[1] Bruce, H W Case of Vincent's Angina in Which the Larynx and Trachea Were Involved Lancet 2 1021 (Oct. 2) 1907

[2] Arrowsmith H Vincent's Angina Involving the Larynx Exclusively Tr Sixteenth Annual Meeting Am Laryng Rhinol & Otol Soc. 16 108 1910

[3] Gomez, F R. Pleuresia purpulent y Gangrena pulmonar Arch. latino-am. de pediat 16 656 (Aug) 1922

OFFICERS OF THE AMERICAN MEDICAL ASSOCIATION—1929-1930

HEADQUARTERS OF THE ASSOCIATION, 535 N DEARBORN ST, CHICAGO

GENERAL OFFICERS

President—M L Harris	Chicago
President-Elect—William Gerry Morgan	Washington, D C
Vice President—Ernst A Sommer	Portland, Ore
Secretary and General Manager—Olin West	Chicago
Treasurer—Austin A Hayden	Chicago
Speaker, House of Delegates—F C Warnshuis	Grand Rapids, Mich
Vice Speaker, House of Delegates—Albert E Bulson	Fort Wayne, Ind
Editor and General Manager Emeritus—George H Simmons	Chicago
Editor—Morris Fishbein	Chicago
Business Manager—Will C Braun	Chicago

BOARD OF TRUSTEES

Joseph A Pettit	Portland Ore	1930
J H J Upham	Columbus Ohio	1930
Thomas S Cullen	Baltimore	1930
E B Heckel Chairman	Pittsburgh	1932
Rock Sleyster	Wauwatosa Wis	1932
J H Walsh Secretary	Chicago	1933
A R Mitchell	Lincoln Neb	1933
D Chester Brown	Danbury Conn	1934
Allen H Bunce	Atlanta Ga	1934

JUDICIAL COUNCIL

Geo E Follansbee Chairman	Cleveland	1930
J N Hall	Denver	1931
Donald Macrae Jr	Council Bluffs Iowa	1932
F W Cregor	Indianapolis	1933
James B Herrick	Chicago	1934
Olin West Secretary ex officio	Chicago	

COUNCIL ON MEDICAL EDUCATION AND HOSPITALS

Louis B Wilson	Rochester Minn	1930
Walter F Donaldson	Pittsburgh	1931
Ray L Wilbur Chm	Washington D C	1932
James S McLester	Birmingham Ala	1933
Emmett P North	St Louis	1934
Reginald Fitz	Boston	1935
M W Ireland	U S Army	1936
N P Colwell Secretary	Chicago	

COUNCIL ON SCIENTIFIC ASSEMBLY

J Shelton Horsley Chm	Richmond Va	1930
John F Lane	New Haven Conn	1931
Frank H Lahey	Boston	1932
Roger S Morris	Cincinnati	1933
L H McKinnie	Colorado Springs	1934

AND EX OFFICIO

The President Elect, the Editor and the Secretary of the Association

COMMITTEE ON SCIENTIFIC EXHIBIT

D Chester Brown Chairman	Danbury Conn
Rock Sleyster	Wauwatosa Wis
J H J Upham	Columbus Ohio

ADVISORY COMMITTEE

George Blumer	New Haven Conn
Paul J Hanzlik	San Francisco
Ludvig Hektoen	Chicago
Urban Maes	New Orleans
Hans Zinsser	Boston
Ralph H Major	Kansas City Kan
J Shelton Horsley ex officio	Richmond Va

COUNCIL ON PHARMACY AND CHEMISTRY

(Standing Committee of Board of Trustees)

L G Rowntree	Rochester Minn	1931
Torald Sollmann	Cleveland	1931
Lafayette B Mendel	New Haven Conn	1931
Reid Hunt Chairman	Boston	1932
W W Palmer	New York	1932
A J Carlson	Chicago	1932
R A Hatcher	New York	1933
E. F Irons	Chicago	1933
H N Cole	Cleveland	1933
W McKim Marriott	St Louis	1934
C W Edmunds	Ann Arbor Mich	1934
Eugene F Du Bois	New York,	1934
Morris Fishbein	Chicago	1935
G W McCoy	Washington D C	1935
E M Bailey	New Haven Conn	1935
George H Simmons	Chicago	1935
W A Puckner Secretary	Chicago	

COMMITTEE ON FOODS

(Special Committee of the Council on Pharmacy and Chemistry

E M Bailey	New Haven Conn
Eugene F Du Bois	New York
Julius H Hess	Chicago
W McKim Marriott	St Louis
L B Mendel	New Haven Conn
C F Powers	New Haven Conn
H C Sherman	New York
Morris Fishbein Chairman	Chicago

COUNCIL ON PHYSICAL THERAPY

(Standing Committee of Board of Trustees)

Ralph Pemberton	Philadelphia
Harry E Mock Chairman	Chicago
W E Garrey	Nashville Tenn.
A S Warthin	Ann Arbor Mich
Francis Carter Wood	New York
A U Desjardins	Rochester Minn
George Miller MacKee	New York
H B Williams	New York
W W Coblentz	Washington D C
R B Dillehunt	Portland Ore.
John S Coulter	Chicago
Robert B Osgood	Boston
Olin West ex officio	Chicago
Morris Fishbein ex officio	Chicago
H J Holmquest Executive Secretary	Chicago

BUREAU OF LEGAL MEDICINE AND LEGISLATION

W C. Woodward Director	Chicago

BUREAU OF HEALTH AND PUBLIC INSTRUCTION

J M Dodson Director	Chicago

BUREAU OF INVESTIGATION

Arthur J Cramp Director	Chicago

CHEMICAL LABORATORY

Paul Nicholas Leech Director	Chicago

LIBRARY

Marjorie Hutchins Librarian	Chicago

SECTION OFFICERS

PRACTICE OF MEDICINE—Chairman Ernest E Irons Chicago Vice Chairman W R. Houston Augusta Ga Secretary Reginald Fitz 721 Huntington Avenue Boston

SURGERY GENERAL AND ABDOMINAL—Chairman Frank H Lahey Boston Vice Chairman Thomas C Orr Kansas City Mo Secretary Fred W Rankin Mayo Clinic Rochester Minn

OBSTETRICS GYNECOLOGY AND ABDOMINAL SURGERY—Chairman J C Masson Rochester Minn Vice Chairman Raymond E. Watkins Portland Ore Secretary Fred L. Adair University of Chicago Medical School Chicago

OPHTHALMOLOGY—Chairman T B Holloway Philadelphia Vice Chairman Joseph L McCool San Francisco Secretary William C Finnoff 1612 Tremont St Denver

LARYNGOLOGY OTOLOGY AND RHINOLOGY—Chairman Robert C Lynch New Orleans Vice Chairman, John B Potts Omaha Secretary Gabriel Tucker University Hospital Philadelphia

DISEASES OF CHILDREN—Chairman William Weston Columbia S C Vice Chairman R S Rowland Detroit Secretary C A Aldrich 723 Elm Street Winnetka Ill

PHARMACOLOGY AND THERAPEUTICS—Chairman C W Edmunds Ann Arbor Mich Vice Chairman Russell M Wilder Chicago Secretary Robert L. Levy 31 East 72d Street New York.

PATHOLOGY AND PHYSIOLOGY—Chairman A H Sanford Rochester Minn Vice Chairman A C Ivy Chicago Secretary J J Moore 55 East Washington Street Chicago

NERVOUS AND MENTAL DISEASES—Chairman George W Hall Chicago Vice Chairman Laurence Selling Portland Ore Secretary Walter Freeman 1801 I Street N W Washington D C

DERMATOLOGY AND SYPHILOLOGY—Chairman William H Guy Pittsburgh Vice Chairman Hiram E. Miller San Francisco Secretary Francis E Senear 55 East Washington Street Chicago

PREVENTIVE AND INDUSTRIAL MEDICINE AND PUBLIC HEALTH—Chairman E. L Bishop Nashville Tenn Vice Chairman, F D Stricker Portland Ore Secretary W G Smillie 55 Van Dyke Street Boston

UROLOGY—Chairman Hermon C Bumpus Jr Rochester Minn Vice Chairman A E Mackay Portland Ore Secretary N G Alcock, 105 East Iowa Avenue Iowa City

ORTHOPEDIC SURGERY—Chairman C B Francisco Kansas City Mo Vice Chairman H W Meyerding Rochester Minn Secretary James S Speed 869 Madison Avenue Memphis Tenn

GASTRO ENTEROLOGY AND PROCTOLOGY—Chairman Julius Friedenwald Baltimore Vice Chairman Dudley A Smith San Francisco Secretary A F R Andresen 88 Sixth Avenue Brooklyn

RADIOLOGY—Chairman Fred M Hodges Richmond Va Vice Chairman William B Bowman Los Angeles Secretary George W Grier, 500 Penn Avenue Pittsburgh

The Journal of the
American Medical Association

Published Under the Auspices of the Board of Trustees

Vol. 94, No. 1 | Chicago, Illinois | January 4, 1930

PROTOZOAN INFECTION OF THE HUMAN BOWEL

A COMPARISON OF LABORATORY AND CLINICAL OBSERVATIONS *

JOHN F. KESSEL, Ph.D.
AND
VERNE R. MASON, M.D.
LOS ANGELES

The relation of human intestinal protozoan infection to disease is a subject that has attracted considerable attention in recent years but as yet has not reached a satisfactory solution. One still finds, on the one hand, a few of the older school who regard infection with *Endameba histolytica* as of no consequence unless associated with acute amebic dysentery or liver abscess. On the other hand, one finds a group who not only attribute many gastro-intestinal disturbances to protozoan infection but also ascribe certain systemic and metabolic disturbances directly to intestinal protozoa.

While these extreme views undoubtedly have been proposed merely as a working hypothesis by those with whom they originated, they have been the means of bringing considerable discredit to the subject of amebiasis in general, in that they have been interpreted by some as having been firmly established. As a consequence, some opponents of the systemic idea have come to regard primary amebic infections in the same negative way that they regard systemic amebiasis. This is indeed unfortunate, for as a result many important cases of intestinal amebiasis have been overlooked.

The whole subject of intestinal protozoiasis, including amebiasis and flagellosis, is in need of further accurate investigation by unprejudiced persons and should be approached from four main angles:

1. Careful histories should be taken of all cases in which laboratory observation reveals protozoa in the stool. These histories should be taken by the unbiased with the express idea in mind of finding, if possible, some cause other than the protozoa to explain the symptoms. In the past it has been far too common an occurrence for a clinician to accept a positive laboratory report of some intestinal protozoan as indicating that the protozoan was actually the cause of the patient's trouble, and treatment has been instituted accordingly, often to the neglect of the real cause of the ailment. Only when other causes have been ruled out, and the protozoa remain as the only etiologic factor, is the clinician justified in assigning the disturbance directly to the intestinal protozoa.

2. Careful laboratory data should be obtained in order to rule out bacterial disturbances, such as tuberculous enteritis and bacillary dysentery.

3. Careful autopsy records and histologic sections should be procured when lesions and disorders are thought to be of protozoan origin.

4. The experimental method should be employed in establishing experimental protozoiasis in suitable animals, e. g., amebiasis, trichomoniasis and giardiasis in puppies and kittens. Monkeys may also be used for observation in the more chronic types of protozoiasis.

One of us (Kessel and Willner[1] and Kessel[2]) has been interested for some time in experimental protozoiasis and also in a thorough correlation of laboratory and clinical observations on this subject. While he was on the staff of the Peking Union Medical College a plan of cooperation between the laboratory and the medical service was worked out with the medical staff and was employed to advantage. The results of this study have never been published since the clinical summaries were not completely tabulated before leaving Peiping two years ago. However, in the General Hospital in Los Angeles opportunity has been afforded for continuation of the study, and the present summary is the first that has been compiled.

Table 1.—*Incidence of Protozoan Infection in California as Compared with Several Other Surveys*

	Number of Cases	Average Examinations per Case*	E. Histolytica	E. Coli	E. Nana	*Iodameba*	Councilmania	Giardia	Chilomastix	Trichomonas
Boeck and Stiles (1923) U. S. P. H. S. Hospitals	8,029		8.0	28.0	23.0	7.5		10.3	9.6	
Kessel (1924-1927) Peking Union Medical College	7,000	3+	10.3	10.8	21.1	4.8	8.2	5.3	1.6	3.1
Svensson (1925) Sweden and Finland hospitals and outpatient departments	770	1	3.0	15.0	10.5	2.1		5.3	1.6	
Kofoid (1926) California State Board of Health	6,834	3.3	13.1	3.1	21.4	2.3	17.7	5.2	6.6	2.0
Kessel (1929) Los Angeles General Hospital	2,731	3	9.8	15.2	16.9	3.2	3.4	4.1	8.3	[illegible]
Reynolds† (1928) College of Medical Evangelists (California)	1,000	4	16.0	6.0	21.0	7.2	19.1	3.7	20.5	[illegible]

* Estimated.

† Unpublished data furnished by Dr. Reynolds of the College of Medical Evangelists.

---

* Read before the Section on Practice of Medicine at the Eightieth Annual Session of the American Medical Association, Portland, Ore., July 12, 1929.

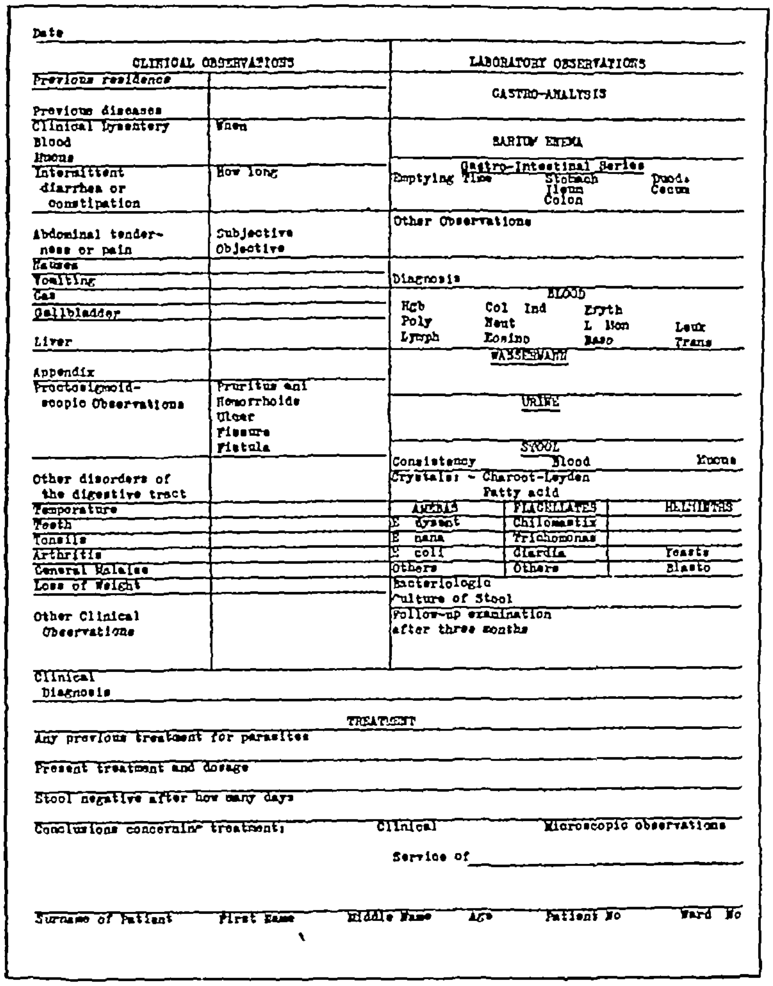
[1] Kessel, J. F., and Willner, O.: Some Clinical and Laboratory Aspects of Amoebiasis with a Preliminary Report on Yatren Treatment, China M. J. 39: 383-396 (May) 1925.

[2] Kessel, J. F.: Amoebiasis in Kittens Infected with Amoebae from Acute and Carrier Human Cases and with Tetranucleate Amoebae of Monkey and of Pig, Am. J. Hyg. 8: 311-354 (May) 1928.

The results show the importance of thorough examination of stools for bacteria and protozoa in hospitals in the United States, especially in regions situated in the warmer climates, and represent a successful departure from ordinary hospital routine

SOURCE OF MATERIAL AND METHODS

In a study of the type here recorded, the greatest cooperation between clinical and laboratory departments is required This is necessary (1) in the collection of fecal samples for laboratory examination, which must be observed fresh, (2) in taking proctologic smears for culture, and (3) in procuring the salient points in the patients' histories



Date

CLINICAL OBSERVATIONS

Previous residence

Previous diseases

Clinical Dysentery — When
Blood
Mucus

Intermittent diarrhea or constipation — How long

Abdominal tenderness or pain — Subjective
Objective

Nausea
Vomiting
Gas
Gallbladder
Liver
Appendix

Proctosigmoidoscopic Observations — Pruritus ani
Hemorrhoids
Ulcer
Fissure
Fistula

Other disorders of the digestive tract
Temperature
Teeth
Tonsils
Arthritis
General Malaise
Loss of Weight
Other Clinical Observations

LABORATORY OBSERVATIONS

GASTRO-ANALYSIS

BARIUM ENEMA

Gastro-Intestinal Series
Emptying Time Stomach Duod.
Ileum Cecum
Colon

Other Observations

Diagnosis

BLOOD
Hgb Col Ind Eryth
Poly Neut L Mon Leuk
Lymph Eosino Baso Trans

WASSERMANN

URINE

STOOL
Consistency Blood Mucus
Crystals: – Charcot-Leyden
Fatty acid

AMEBAS	FLAGELLATES	HELMINTHS
E dysent	Chilomastix	
E nana	Trichomonas	
E coli	Giardia	Yeasts
Others	Others	Blasto

Bacteriologic Culture of Stool

Follow-up examination after three months

Clinical Diagnosis

TREATMENT

Any previous treatment for parasites

Present treatment and dosage

Stool negative after how many days

Conclusions concerning treatment: Clinical Microscopic observations

Service of__________

Surname of Patient First Name Middle Name Age Patient No Ward No

History sheet for protozoan cases

We feel that the present study yields especially fair conclusions because the laboratory observations and clinical observations have been made by independent workers Further, histories have been taken by independent internists on different services and have merely been summarized and the facts correlated by us There has thus been little opportunity for prejudiced conclusions

SOURCE OF PATIENTS

The hospital patients in this study were all ill and came to the hospital for advice Apart from 18 per cent who were Mexicans, most of them did not give a history of residence outside the United States

Of the series here studied, 60 per cent of all groups presented gastro-intestinal symptoms and stool examinations were made as part of the routine In this large group there are included those exhibiting actual dysentery or diarrhea, constipation with and without vague abdominal distress, the so-called functional neuroses of the gastro-intestinal tract, the definite lesions of the gastro-intestinal tract, and diseases with secondary gastro-intestinal manifestations, such as pellagra or tabes It also included a number of patients under par in whom a definite and satisfactory diagnosis, apart from colitis, could not be made in many instances

A small group of arthritic cases has been observed The correlation of *E histolytica* infection with arthritis is small in our series thus far, but we feel that we have an insufficient number to warrant conclusions, and, since further studies are being made on this subject, the data will be withheld for later presentation

LABORATORY METHODS

Standard laboratory methods have been employed for the detection of bacteria and protozoa For the differentiation of *Bacillus dysenteriae*, standard sugar reactions and agglutination tests were employed In examination for protozoa, a combination of the fresh smear method with saline solution and iodine-eosin and the permanent smear method in Haidenhain's iron-hematoxylin has been used throughout In addition, a large percentage of the fecal samples have been subjected to the culture method in the standard Ringer's-egg-serum medium In a few cases known to be positive and others to be negative for *E histolytica*, the complement fixation method described by Craig[3] was employed The results were promising, though not conclusive in all cases

Table 1 shows the incidence of hospital protozoan infection in California as compared with several other hospital surveys of importance and the California State Board of Health report The estimated summary of Boeck and Stiles[4] for hospitals in the United States is purely relative since the results are obtained from a variety of sources without the employment of standardized methods Since similar methods have been employed in the other surveys, they are comparable except for the fact that the average number of examinations per case varies in the different surveys This is especially low in the results of Dr Svensson[5] in Sweden, as she records only a single examination per patient If her figures had been compiled following three examinations per case her results would probably have been doubled, at least for *E histolytica* Several interesting comparisons may be drawn from a study of this table

1 Svensson's report is further evidence that the intestinal protozoa are not confined to the tropics but are found in fairly high percentages even in countries as far north as Scandinavia

---

[3] Craig C F Complement Fixation in the Diagnosis of Infection with Endomoeba Histolytica Am J Trop Med 8 29 38 (Jan) 1928

[4] Boeck W C and Stiles C W Studies on Various Intestinal Parasites (Especially Amoebae) of Man Bull 133 Hyg Lab U S P H S 1923

[5] Svensson R A Survey of Human Intestinal Protozoa in Sweden and Finland Parasitology 20 237 249 (Oct.) 1928

2 The reports by Kofoid, Kessel and Reynolds compare favorably and show that the incidence of intestinal protozoan infection in California is higher than the estimated incidence of infections by Boeck and Stiles[4] in hospitals throughout the United States

3 Incidence of protozoan infection is on the whole lower in Los Angeles General Hospital than in the Peking Union Medical College Hospital *E histolytica* is 6 5 per cent lower *Chilomastix* and *Trichomonas,* however, are slightly higher in Los Angeles Kofoid[6] and Reynolds (1928) show a low incidence of *E coli* and a high incidence of *Councilmania lafleuri,* while Kessel (1929) shows a higher incidence of *E coli* than of *Councilmania lafleuri* These figures demonstrate that the personal factor enters into the differentiation between *E coli* and *Councilmania lafleuri,* Kofoid preferring to give the benefit of the doubt in slightly dispersed karyosomes to *Councilmania,* while we prefer to designate as *Councilmania* only those protozoa having nuclei with definite, heavily dispersed karyosomes and conclude that the karyosomes showing slight dispersion are merely division stages of *E coli* Otherwise, one will find many mixed cases of *E coli* and *Councilmania* and will note considerable variation from day to day in the same patient

TABLE 2—*Comparative Value of Smear and Culture Method in Laboratory Diagnosis for Intestinal Protozoa*

Infection	Total	Smear + Culture +	Smear + Culture —	Smear — Culture +
F histolytica	77	32 4%	64.8%	2 6%
Chilomastix	164	59 7	9 1	31 1
Trichomonas	160	51 3	3 1	42 5

4 Boeck and Stiles show an incidence of *Giardia* infection of 10 3 per cent while all the other surveys show a much lower incidence of infection with *Giardia*

Table 2 shows the comparative value of the common smear and cultural method in Ringer's-egg-serum medium for *E histolytica, Chilomastix* and *Trichomonas* In this series it will be seen that the smear method is more effective in detecting *E histolytica* than the culture method and that as a result of the culture method only 2 6 per cent of cases were detected which otherwise would have been overlooked

Chilomastix and *Trichomonas,* however, present quite a different picture and show that 31 1 per cent of the cases were detected by culture which were overlooked by the smear method, and 42 5 per cent of *Trichomonas* cases were diagnosed positive by the culture method which were not previously observed by direct smear St John[7] shows much more promising results in the employment of the culture method for routine diagnosis of amebiasis One wonders whether his later experience has verified his earlier conclusions and whether he employs the culture method in preference to the smear method

VALUE OF BACTERIAL CULTURE IN PROTOZOIASIS

The question of performing bacterial cultures in cases found to be positive for intestinal protozoa cannot fail to impress one as being of value in regions where epidemics of bacillary dysentery are common Bacteriologic culture was performed as a routine in cases of amebic dysentery in Peiping, where the ratio of bacillary dysentery to amebic dysentery was about ten to one Knowles[8] has also raised the question of a possible relation between acute amebiasis and streptococcus infection, and also the question of whether diarrheas in which *Trichomonas* were found were not actually caused by *B dysenteriae* rather than by *Trichomonas*

In this country, where bacillary dysentery is relatively rare one would question the merit of performing a routine bacteriologic culture in all positive protozoan cases However, in order to collect accurate data on this point such a routine was established Instead of cultures being taken only of the stool for bacteria, smears were made whenever possible at the time of proctoscopic examination and cultures of these smears taken for bacteria

Table 3 shows the bacteriologic cultures yielded by fifty-nine cases of *E histolytica* thirty-three cases positive for *Giardia* forty-three cases positive for *Chilomastix,* and forty-eight cases positive for *Trichomonas* It will be seen that gram-positive cocci, either streptococcus or the gram-positive diplococcus of Bargen, have been found in a few instances and also that *B dysenteriae* has been present, most commonly in *Giardia* infections, in children

However the correlation of protozoan and bacteriologic infection was not sufficiently high to obscure or make negative the pathogenic role of the protozoa

During the period of this investigation, sixty cases of *B dysenteriae* Flexner, Shiga or Morgan have been detected in the Los Angeles General Hospital Of these three have also been positive for *E histolytica* five for *Giardia,* three for *Chilomastix* and two for *Trichomonas*

In a series of cases negative for intestinal protozoa, used as controls, *B welchii* showed a similar incidence to that found in the series recorded in table 3 This would indicate that there is no special correlation between this organism and intestinal protozoan infection

CORRELATION OF INTESTINAL PROTOZOA WITH CLINICAL MANIFESTATIONS

In this study, just as soon as a positive laboratory observation for some intestinal protozoan was obtained, a report of it, together with a copy of the accompanying history sheet for protozoan cases, was sent to the ward As much special work e g gallbladder dye series proctoscopic examination, gastro-analysis and roentgenograms of the gastro-intestinal tract series, was accomplished in every case as was consistent with the case in question

TABLE 3—*Percentage of Positive Bacteriologic Observations Among Patients Harboring Intestinal Protozoa*

	Number of Cultures	Gram Positive Cocci Streptococcus or Bargen Diplococcus	B Dysenteriae Shiga Flexner or Morgan	B Proteus B Alcaligines and B Paracoli	B Welchii
F histolytica	59	7%	7%	11%	21%
Giardia	[illegible]	None found	10%	15%	[illegible]
Chilomastix	43	2%	6%	12.5%	14%
Trichomonas	48	1%	5%	8%	1 %

Tables 4 and 5 have been compiled from a study and classification of the data derived from patients histories

In this series ten cases have shown a typical tropical or amebic dysentery and amebas have been detected in the pus from typical amebic liver abscess in four other cases Such cases give no doubt as to their origin It

---

6. Kofoid C. A Statistical Summary of Persons Examined for Protozoa, in California State Board of Health Twenty Ninth Biennial Report Sacramento Calif California State Printing Office 1926 p 93

7 St John J H Practical Value of Examination for Endamoeba Histolytica by Culture J A. M A 86: 1272 (April 24) 1926

[8] Knowles R An Introduction to Medical Protozoology Calcutta 1928

is the more chronic type of case with which we are especially concerned in this study.

Two cases of this series were diagnosed as Hodgkins' disease. One showed a small trace of *E. histolytica* in the stool and the other did not. Sections from lymph glands, taken by biopsy and at autopsy, did not reveal any organisms that gave the characteristic appearance of amebas.

The proctoscopic examinations have not yielded as high an incidence of ulcerated colons as was hoped. However, when one considers the work of previous investigators (Rogers[9] and Clark[10]) one appreciates that the greatest number of ulcers in cases of chronic amebiasis are situated in the upper colon and cecum, beyond the reach of the proctoscope.

In our summary, the cases have first been grouped into six groups as follows: 1. Negative for protozoa, a series which may be looked on as a control group. In all these cases, four or more examinations have been made for protozoa and the chances for a positive protozoan infection are consequently lessened. 2. Harmless protozoa, a series including cases positive for *E. coli*, *E. nana* or *Councilmania lafleuri* without the presence of other protozoa. 3. A series of cases positive for *E. histolytica*, most of which did not have complicating infection of flagellates. 4. A series of cases positive for *Giardia* without *E. histolytica* or other flagellates. 5. A series of cases positive for *Chilomastix* without *E. histolytica* or other flagellates. 6. A series of cases positive for *Trichomonas* without *E. histolytica* or other flagellates.

TABLE 4.—*Distribution of Protozoan Infection Among Two Clinical Groups* *

	Total Number of Cases	Number of Cases in Which a Disease Other than Colitis Is Present and Which Is Adequate to Explain Whole Clinical Syndrome		Number of Cases in Which No Disease Other than Colitis Is Present as an Adequate Explanation of Clinical Syndrome	
		Number	Per Cent	Number	Per Cent
Negative for protozoa	200	164	82	36	18
Harmless protozoa E. coli, E. nana, Councilmania	200	168	84	32	16
E. histolytica	100	48	48	52	52
Giardia	50	34	68	16	32
Giardia (adults)	30	24	75	8	25
Giardia (children)	20	10	50	10	50
Chilomastix	100	73	73	27	27
Trichomonas	50	34	68	16	32

* In one the diagnosis was adequate to explain the clinical syndrome and in the other the diagnosis other than colitis was insufficient to explain symptoms.

These six groups were then studied with reference to the percentage of distribution of various types of symptoms within each group.

Table 4 shows the comparison among two major clinical groups, one in which some disease other than colitis was present and which in itself appeared adequate to explain the whole clinical picture. The second group was a clinical group in which no disease other than colitis was present as an adequate explanation of the syndrome.

The word colitis is used here to mean literally "disease of the colon." The usual clinical manifestations of this group are malaise, loss of weight, usually not recent, diarrhea at times, and colonic distress with tenderness and gas.

A study of the two groups will show several interesting comparisons. 1. Those negative for protozoa and those harboring the harmless protozoa were distributed within the two groups about equally, thus supporting the conclusion that cases positive for *E. coli*, *E. nana* and *Councilmania lafleuri* do not show a higher percentage of colitis symptoms than cases not presenting protozoa. It may be questioned why *E. coli*, *E. nana* and *Councilmania lafleuri* are placed together in a single class. Each species was studied singly first and there was practically no variation in their individual distributions. Subsequently they were classed together.

2. Cases positive for *E. histolytica* yielded 52 per cent in the colitis group or three times the number afforded by the negative group.

3. Of the cases positive for *Giardia*, 32 per cent fell in the colitis group. This is about twice as high as the negative cases but 20 per cent less than the *E. histolytica* cases. A further division of the cases positive for *Giardia* into adults and children shows that colitis symptoms were encountered twice as frequently in children as in adults. The series is small but supports the view that giardiasis symptoms are found much more commonly in children than in adults.

4. Cases positive for *Chilomastix* showed 27 per cent with symptoms of colitis. This is about twice as many as were found in those negative for protozoa or in those in which commensal protozoa were harbored. It is about half as high as the colitis group in the cases positive for *E. histolytica*.

5. Thirty-two per cent of the cases positive for *Trichomonas* fell into the colitis group. In fact, there is little variation in the colitis group between the distribution of *Giardia*, *Chilomastix* and *Trichomonas*.

In conclusion, on the basis of data in table 4 one may state that in a series of cases which did not give evidence of any disease other than colitis as an adequate explanation of the clinical syndrome, first, those positive for *E. histolytica* were three times as frequent as those negative for protozoa or positive for commensal protozoa, and, second, those positive for flagellates were about twice as frequent as those negative for protozoa or positive for commensal protozoa.

From a statistical consideration it seems that one is justified in assuming that the organism found in this more frequent association may be in some way responsible for the colitis symptoms. Such a contention, however, must have experimental support.

Table 5 shows the frequency with which cases (1) negative for protozoa in which (2) commensal protozoa, (3) *E. histolytica*, (4) *Giardia*, (5) *Chilomastix* and (6) *Trichomonas* are present are associated with certain clinical symptoms important in the study of gastro-intestinal diseases.

Throughout one sees little difference in the percentages between those negative for protozoa and those in which the harmless protozoa are present.

The following considerations from this table are of interest:

1. *Endameba histolytica* is the organism most commonly associated with diarrheic and colitis symptoms, it being present in 66 per cent of the cases. *Giardia* was present in 44 per cent, *Chilomastix* in 31 per cent and *Trichomonas* in 34 per cent, while the group negative for protozoa give an incidence of 26.5 per cent with such symptoms.

2. *E. histolytica* is found more frequently associated with cases showing a chronic colitis than with cases showing an actual dysentery or diarrhea.

---

[9] Rogers, L.: Bowel Diseases of the Tropics, Oxford Medical Publications, 1921.

[10] Clark, H. C.: The Distribution and Complications of Amoebic Lesions Found in One Hundred and Eighty Six Postmortem Examinations, Proc. Internat. Conf. on Health Problems in Tropical America, Boston, United Fruit Company, 1924, pp. 365-379.

3 Forty per cent of the cases in which *E histolytica* was present show a chronic colitis, while only 20 per cent of those positive for *Giardia*, 21 per cent of those positive for *Chilomastix* and 18 per cent of those positive for *Trichomonas* show this symptom

4 There is no particular increase in any group of infections in the "spastic colitis" group, and these all compare favorably with the negative series This would support the hypothesis that "spastic colitis" is not etiologically related to inflammatory disease, at least to any produced by protozoa

5 In about 25 per cent of the patients in all groups the bowels are constipated This does not support the notion so often expressed that constipation is a special symptom of amebiasis

6 No single protozoan is associated frequently with gallbladder disease and duodenal ulcer in this series with the exception of *Chilomastix*, which is high in the gallbladder group and *Trichomonas*, which is high in the duodenal ulcer group Lynch[11] observes "that a clinical diagnosis of chronic cholecystitis was recorded in about twice as many of the carriers of *Trichomonas* and *Chilomastix* as in the flagellate free" One certainly would not conclude that gallbladder disease and duodenal ulcer are caused by either *Chilomastix* or *Trichomonas* It would seem feasible, however, to assume that these protozoa are present in conditions associated with hyperacidity and hypo-acidity in such high percentages because they possess a greater range of culture variability than the other protozoa in question We have found *Chilomastix* and *Trichomonas* growing in mediums showing a range in p_H from 7 7 to 3 8

TABLE 5—*Frequency with Which Cases Are Associated with Diarrhea Chronic Colitis Constipation Gallbladder Disease and Duodenal Ulcer*

	Number of Cases	Colitis with Diarrhea or Dysentery*		Chronic Colitis without Diarrhea or Dysentery		Diarrhea and Colitis†		Spastic Colitis		Constipation		Gallbladder Disease		Duodenal Ulcer	
		Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent
Negative for protozoa (4 to 6 examinations)	200	28	14	25	12.5	53	26 5	15	7.5	49	24.5	3	1.5	15	7 5
Harmless protozoa E coli E nana Councilmania	200	15	7.5	28	14	43	22.5	17	8.5	45	22.5	8	4	6	3
E histolytica	100	26	26	40	40	66	66	7	7	24	24	3	1.5	4	4
Giardia	50	12	24	10	20	22	44	1	2	12	24	2	4	3	6
Chilomastix	100	10	10	21	21	31	31	7	7	29	29	13	13	8	8
Trichomonas	50	8	16	9	18	17	34	3	6	10	20	3	6	8	16

* Exclusive of bacillary dysentery

† Percentages in this column are higher than in table 4 because they take into account diarrheic and colitis symptoms that may be superimposed in cases presenting an otherwise adequate diagnosis

SUMMARY AND CONCLUSIONS

1 Patients in the Los Angeles County General Hospital, 60 per cent of whom showed colitis symptoms, gave an incidence of intestinal protozoan infection similar to that in cases examined by Kofoid in the California State Board of Health and somewhat higher than that estimated by Boeck and Stiles for hospitals throughout the United States

2 Routine culture of stools in Ringer's-egg-serum medium has not increased appreciably the percentage of *E histolytica* infection over examinations made by the standard smear method, though both *Chilomastix* and *Trichomonas* have been noticeably increased

3 Routine bacteriologic culture of material from proctoscopic smears and fresh stools, for *B dysenteriae* and gram-positive cocci from cases found to be positive for intestinal protozoa, has shown that these bacteria are present in a low percentage of such cases and when present may have a bearing on the history They are insufficiently numerous in Los Angeles, however to obscure the clinical picture of protozoiasis in a high percentage of cases *B dysenteriae* has been found most commonly in *Giardia* infections among children

4 In a comparison of hospital cases positive for intestinal protozoa with cases negative for intestinal protozoa the following general deductions may be drawn

(*a*) Patients harboring *E coli*, *E nana* and *Councilmania lafleuri* do not exhibit gastro-intestinal symptoms more frequently than those negative for intestinal protozoa

(*b*) Patients harboring *E histolytica* exhibit colitis symptoms about three times as frequently as those negative for intestinal protozoa This fact emphasizes the importance of routine examination for *E histolytica* in patients who exhibit gastro-intestinal symptoms

(*c*) The group positive for flagellates (*Giardia*, *Chilomastix* and *Trichomonas*) is associated more frequently with gastro-intestinal symptoms than the groups negative for protozoa or positive for the commensal amebas This association, however, is less frequent than in the group positive for *E histolytica*

(*d*) Twice as many children found to harbor *Giardia* exhibited gastro-intestinal symptoms as did the adults who harbored *Giardia*

(*e*) 'Spastic colitis' and constipation are not associated more commonly with the groups harboring any intestinal protozoa than with those negative for intestinal protozoa

(*f*) Cases showing symptoms of gallbladder disease and duodenal ulcer show an increased incidence of *Chilomastix* and *Trichomonas* infection

Los Angeles General Hospital

ABSTRACT OF DISCUSSION

DR. J A MCINTOSH Memphis I am interested in finding protozoa in surgically removed appendixes Many times I am confronted with tissue removed by surgery clinically diagnosed as inflammatory and have found it to be noninflammatory I have been embarrassed in some instances knowing that the removal of such an organ was done because the patient suffered from abdominal symptoms yet when the material was placed in my hands I was unable to demonstrate the presence of inflammatory change This experience led me to consider the contents of the gastro intestinal tract or the appendix and the contents of the appendix In a series of 310 surgically removed appendixes I found flagellates eight time These flagellates were identified as *Chilomastix mesnili* In addition to that I found *Endamoeba histolytica* twelve times sometimes associated with the acute inflammatory process, sometimes associated with a chronic process, and sometimes present without any demonstrable microscopic evidence of inflammation It led me to consider whether the so called harmless type of protozoan occasionally present in the intestinal contents was as harmless as we seemed to believe because of the absence of invading power I have noticed this If individuals who have a tendency to allergy happen to carry the so called harmless types of protozoa, they have eczema and their nervous system is extremely upset I recall more than one case in which the patient complained only of nervousness and I found the intestinal contents heavily charged with flagellates As soon as the flagellates were removed, the individual s condition was improved As to the relationship of climate to protozoal infestations, we find them in Memphis in large numbers Individuals harboring animal parasites have low metabolic rates The cutaneous manifestations of the host of protozoal infestations are often confusing It has been my experience that one can demonstrate eosinophilia in the host of animal parasites The percentage of eosinophilia varies with the hypersensitive state of the individual As to the identification of the protozoa, I have used Dr Craig s improved culture method and have been able to cultivate the flagellates, and also the amebas, but not as often as I am able to pick them up in the moist mount in smear I employ vital staining and use a mixture of glycerin, iodine and eosin stain before I fix them I am fairly successful in identifying them in this way

---

[11] Lynch K. M The Flagellated Protozoa of the Intestine Am. J Trop Med. 8 345 352 (July) 1928.

Dr Frank Smithies, Chicago We are living in an age of so called colitis Some one recently said that for all his patients the diagnosis of colitis was advanced in 40 per cent The authors have emphasized one important point, namely, that when a diagnosis of colitis is made it should not be the end but the beginning of the investigation, because in a number of these chronically recurring instances of 'colitis' we deal with protozoic infestations of the bowel or some of its associated appendages One has been mentioned by Dr McIntosh—the appendix I have already placed on record thirty instances of parasitosis of the biliary passages and the gallbladder in which, at the time of operation, I found the same protozoa in the gallbladder contents that I found on duodenal drainage. These were instances of frequent recurrences after the parasite had been eradicated from the alimentary tract We should get out of our minds the idea that amebiasis means "dysentery" When the individual carries the protozoa in the encysted stage, he may have no symptoms whatever Yet that individual, when the cysts develop to vegetative organisms, has definite evidences of active colitis, frequently associated with diarrheic stools or actual diarrhea The reason California boasts many of these conditions is that observers have been looking for the parasites They are widespread Amebic colitis in Eskimos has been recorded In cities adjacent to rural communities one has no difficulty in finding intestinal protozoa We have found about 300 instances among 3,600 patients Many of these patients were being treated for "colitis" by vaccines, serums, diet and medicines The infestation is largely spread by carelessness about drinking water and by the free ingestion of raw roughage and fruit As a result of the publicity emanating from sanatoriums and newspaper "health" columns, there are many roughage eaters These roughage eaters are potential manure eaters, because garden truck is contaminated during growth by the dejecta of barnyard animals, or by impure water The problem which we are facing with regard to the treatment of patients is serious, not only is there "colitis" but instances occur in which the colon has become scarred deformed and deficient in function after the organisms have been eradicated Systematically, the liver, the brain, the testicles, the joints and various parts of the body may be affected The stools are negative, but the parasitosis and its consequences remain

Dr J F Kessel Los Angeles Dr McIntosh has collected some interesting data, and I should judge has a fertile field in his part of the country for further investigations of significance Dr Smithies experience apparently leads him to accept the conclusion that most of the intestinal protozoa are pathogenic and that they may produce secondary systemic infections as well as primary foci of infection Although we recognize the importance of the role played by certain of the intestinal protozoa in disease and have tried to emphasize what we consider to be some of the significant points in our paper, our experience has not led us to accept as proved all of the generalizations indicated by Dr Smithies There are two points in our paper which I should like to clarify The first concerns the meaning we have given to the word "infection" We have used infection to mean the establishment of parasites within a host without reference to disease conditions which may or may not result Such parasites may multiply within the host, for example, protozoa multiply within the intestinal tract Infection is thus differentiated from infestation, which indicates a condition in which organisms are harbored and do not multiply within the host, for example, hookworm does not multiply in the intestinal tract Second, with reference to the pathogenicity of flagellates, we do not want to give the impression that we have said definitely that the intestinal flagellates are pathogenic. In a certain percentage of instances they are associated with cases that present clinical symptoms, and the evidence of the past is certainly just as strongly in favor of their pathogenicity as it is in favor of their being nonpathogenic The question, however, is still open for consideration and needs investigation I think it should be investigated together by the clinician, by the pathologist, and by the experimentalist In some of my experimental work in kittens, I have observed invasion of trichomonads into the tissue In other cases, however, there was no tissue invasion but merely a necrosis and catarrhal inflammation of the mucosa I have also seen an autopsy in the Los Angeles General Hospital in which trichomonads were present in great numbers and in which the cecum presented the characteristic mucoid condition just described for kittens There was however, no invasion of the tissue by the flagellates Wenyon, on the other hand, has found invasion of trichomonads into the human bowel, although he suggests that the invasion may have been the result of postmortem change I do not think that we have sufficient evidence collected to make a definite statement concerning the pathogenicity of the flagellates

ASTHMA DUE TO A FUNGUS—ALTERNARIA *

J G HOPKINS M D
RHODA W BENHAM, M A
AND
BEATRICE M KESTEN M D
NEW YORK

Cooke[1] was probably the first to emphasize the importance of dust as a cause of asthma In 1922 he reported that in 327 cases of asthma a reaction to dust of diagnostic importance was found in 109, or 33 per cent He found the activity of the dust was diminished when it was heated at 100 C in a sealed tube and was destroyed when it was boiled in an open vessel He was unable to correlate this reaction in his patients with their sensitization to known constituents of dust He states in his conclusions "The new procedure of testing dust extracts has shown the presence of a substance in common house dusts which is an important factor but the nature and source of which are as yet unknown"

Cooke's observations on the frequency of dust sensitiveness in asthma have been abundantly confirmed McLaughlin[2] reported that, of 1,186 patients, 63 per cent were dust positive and 126 reacted to dust alone Rowe[3] reported 160 cases, of which 42 per cent were dust positive He thought the reactions were probably explainable by the presence in the dust of such substances as animal dander, hair, orris or glue and

---

* From the Department of Dermatology and the Laboratory for Medical Mycology Columbia University College of Physicians and Surgeons

[1] Cooke R A J Immunol 7:147 (March) 1922

[2] McLaughlin J S Skin Tests in Patients with Asthma J A M A **89** 663 (Sept 10) 1927

[3] Rowe A H House Dust in Etiology of Bronchial Asthma and of Hay Fever Arch Int Med **39** 498 (April) 1927

extracts gave positive percutaneous reactions Prausnitz-Kustner tests with the patient s serum and the extract of *Alternaria* 1305 were made in three normal individuals and were positive Attempts at passive sensitization of guinea-pigs to *Alternaria* failed

In order to determine whether these skin reactions were significant, inhalation tests were made with the preparations listed in table 2 The patient cooperated wholeheartedly in submitting to these tests, some of which were followed by days of distressing asthma

Table 2—*Preparations Used in Inhalation Tests*

Preparation	Reaction
Alternaria 1305 (cellar)	
Dry powder unheated	Marked asthma
Dry powder heated at 56 C 24 hours	Mild asthma
Dry powder heated at 100 C 2 hours	No symptoms
Carbon dioxide extract heated at 56 C 1 hour	No symptoms
Broth from 3 months culture filtered through Berkefeld filter	Severe asthma
Broth culture as above heated at 100 C 1 hour, sealed tube	Trace of asthma
Broth culture as above heated at 100 C 1 hour open tube	No effect
Broth culture distillate obtained under diminished pressure at from 40 to 50 C	No effect
Circinella spinosa 1102	
Dry powder heated at 56 C 48 hours	Marked asthma
Penicillium glaucum (stock)	
Spores unheated	No symptoms
Paecilomyces varioti (room)	
Dry powder heated at 56 C 48 hours	No symptoms
Penicillium 1229 (room)	
Dry powder heated at 56 C 48 hours	No symptoms
Aspergillus niger (stock)	
Heated at 100 C 1 hour	No symptoms
Cephalothecium roseum (stock)	
Dry powder, heated at 56 C 48 hours	No symptoms

The inhalation tests were made in the case of fluids by spraying with an atomizer while the patient inhaled vigorously and in the case of powder by blowing powder into the mouth while the patient inhaled

Typical attacks of asthma began a few minutes after inhalation of spray from a broth culture of *Alternaria* or of powder prepared by drying and grinding the fungus Heating at 100 C practically destroyed the activity of the preparations and prolonged heating at 56 C weakened them This heat sensitivity is of interest because it is similar to that observed by Cooke[1] in dust extracts

Control tests with the substances which produced attacks made on a normal individual not subject to asthma, produced no effect

In an attempt to determine whether the asthmatic attacks were produced by flying spores or by some volatile substances given off by *Alternaria* a distillate was prepared from a broth culture by boiling it under reduced pressure at a temperature of from 40 to 50 C This distillate had an odor which the patient regarded as characteristic, but inhalation of the spray did not produce symptoms

The patient showed the most marked sensitiveness to *Alternaria* and this fungus also incited asthma He showed, however, definite skin sensitiveness to *Cephalothecium Paecilomyces* and *Penicillium*, preparations of which failed to induce asthma Conversely, one of the *Circinella* provoked asthma but failed to give a skin reaction This lack of complete correlation is in accordance with numerous observations that skin reactions in asthmatic persons give only a lead toward the identification of the causative agent

Comparison of different preparations indicated that unheated filtered broth from an old culture was the most effective preparation The fact however, that the patient reacted to the washed felt when dried and powdered or extracted, indicated that the reaction was due to some substance in the fungus rather than to a substance which it produced in the culture medium It seemed indisputable that some substance in at least one fungus (*Alternaria*) could incite asthma in this patient In view of the fact that the spores of these fungi are small that they travel great distances and that they are so omnipresent that culture mediums cannot be exposed for any length of time to the air in most localities without the deposition of some of these spores, it seems probable that the spontaneous attacks in this patient were due to the inhalation of fungous spores The patient's own observations as to the localities and conditions in which he was most subject to attacks bear out this hypothesis

DESCRIPTION OF FUNGUS

Alternaria is a common form genus of the hyphomycetous fungi, belonging to the family *Dematiaceae*[7] The genera of this family are characterized by the presence of dark or smoky cell walls which give the colony a dark, almost black appearance The genus *Alternaria* has large, dark brown, many celled, muriform spores, usually borne in chains on well differentiated colored conidiophores These spores are widely distributed in nature since the species grow on various sorts of decaying material The mold is often obtained as a contaminant in Petri dish cultures, though perhaps not as frequently as *Aspergillus* or *Penicillium* Species of *Alternaria* are frequently referred to under the name *Macrosporium*, and many species have been described in botanic literature The characteristics of the fungus given are usually insufficient for identification, so that the determination of the species from a culture specimen is difficult unless its natural host or habitat is known

Elliott[8] has made one of the most thorough studies of the genus *Alternaria* and has arranged the various species in groups based primarily on spore measurements The description of the genus, as given by Elliott, is as follows

> Alternaria, Nees Conidiophores solitary or fasciculate, erect or subdecumbent simple or branched generally short, colored Conidia muriform often with few longitudinal septa, ovate, obclavate, or elongate, always with more or less definitely pointed apex, often long beaked, colored, under favorable conditions forming chains

In the few cases so far proved by culture experiments, the species represent the conidial or imperfect stage of the genus *Pleospora*, one of the *Ascomycetes* (Culture 1305, with which the experiments in connection with the causation of asthma were conducted, may, however, belong to some other genus of *Ascomycetes* and the connection must be proved by culture experiments)

Species of *Alternaria* may be included in the group of fungi imperfecti which are prone to mutate or saltate in culture, so that two or more distinct types of mycelial growth develop in a culture originally derived from a single spore By isolating and transferring fragments of hyphae (or *spores if they are present) from the two* kinds of mycelium, the two races can be cultivated separately, whereby each shows its peculiar characteristics to better advantage Bonde,[9] in growing a chromogenic race of *Alternaria solani*, obtained a saltation appearing as a darker, faster growing sector in plate cultures Transferring strains from plates to tubes and vice versa is apt to result in a saltation Roberts,[10] working with *Alternaria mali*, obtained two distinct

Table 3—*Spore Measurements* *

Series	Width	Length	Age Days
I G	10 13	28 63	4
II G	10 25	25 46	7
III G	9 58	21 31	10
IV R	7 35	27 62	5
V R	8 71	23 71	9
Average race G	9.98 by 26 13		
Average race R	8 03 by 27 16		

* These figures represent for each series the average for 100 spores expressed in microns.

---

[7] We are indebted to Dr B O Dodge and Dr Margaret B Church for advice and assistance *in the mycologic work*.

[8] Elliott J A. Taxonomic Characters of the Genera Alternaria and Macrosporium Am J Bot. **4**: 439 476 1917

[9] Bonde R Physiological Strains of Alternaria Solani, Phytopathology **19**: 533 548 1929

[10] Roberts J R. Morphological Characters of Alternaria Mali J Agri. Research **27** *699 708 1924*

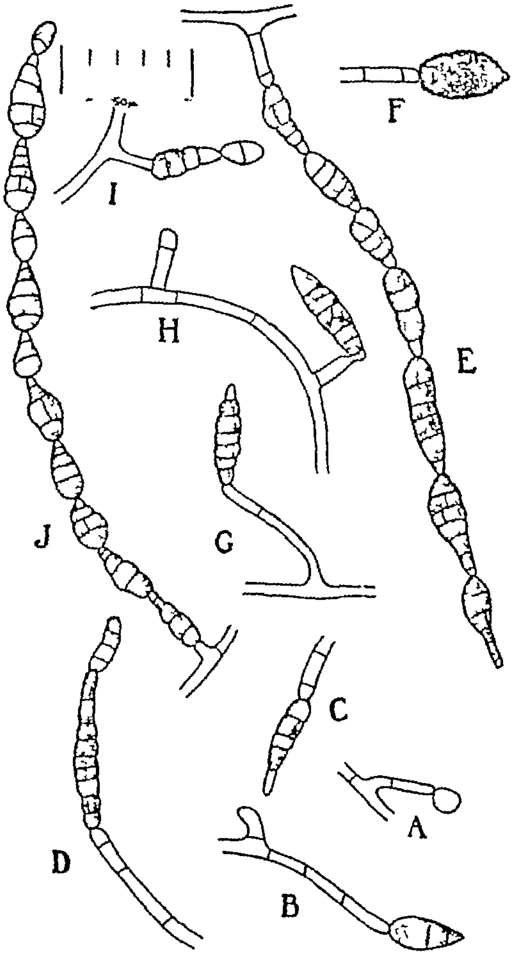
races as the result of saltations in a culture derived from a single conidium Saltant A was unstable for ten generations and then became constant, while it required fifty-seven transfers to obtain a stable race of the second saltant B The production of larger conidia by race B, Roberts thinks, is incident on their location near the surface of the medium

During the progress of our work on asthma, *Alternaria,* culture 1305, was grown on a honey agar and a Sabouraud's medium There was no indication that the stock culture was not a pure culture of a single form of *Alternaria* When, however, the fungus was transferred to corn-meal agar, there appeared to be two types of mycelial growth, suggesting that perhaps a mutation had occurred as the result of changing the medium At the center of the culture there was an excessive development of a grayish green to olivaceous mat of fluffy aerial hyphae such as characterized the original culture A great many chains of conidia were formed in this region Within the medium, and particularly at the margin of growth the mycelium was coarser and of a reddish brown In order to prove whether or not the culture was mixed and now contained two different mycelia or races of *Alternaria,* it was necessary to make single spore cultures A number of single conidia were isolated with the aid of a binocular dissecting microscope from the greenish central area of growth, and after they had germinated they were transferred to tube cultures Although the reddish brown mycelium appeared to be producing some conidia, it was impossible to tell this with certainty It was necessary to tease out fragments of hyphae a few cells in length After these had sprouted out so that tip ends of the new branches could be cut off and transferred to tubes, the original fragments were mounted on slides where they could be examined with high power to prove that the branches of hyphae transferred actually came from the reddish brown fragments In this way two distinct races of *Alternaria* have been obtained from the original culture 1305 One race, G, develops a characteristic green to olivaceous mycelium and an abundance of fluffy aerial hyphae Race R produces only a coarse reddish brown mycelium, and aerial growth is not noticeable

In the absence of knowledge of the natural plant host, it is necessary to rely on spore measurements in the identification of the species of *Alternaria* which we obtained in the case reported here The spores for measurement were taken from corn-meal agar tubes and placed on a slide in a drop of mounting fluid which does not alter the size of the spores All of the cultures represent single spore strains In all, 500 spores were measured, in five series of 100 spores each Each series consisted of four sets of twenty-five spores each set being taken from separate culture tubes The mean width and length for the 100 spores of each series are shown in table 1

These measurements show that there is a comparatively small difference in the size of the spores of the two races and would place our species in Elliott's *Alternaria tenuis* group, for which he gives the limit of spore measurements as follows width, from 7 to 20 microns, length, from 11 to 50 microns The types of spores found in the two strains G and R are shown in the accompanying illustration In *E* and *J,* chains of spores from races G and R, respectively are shown The spores of these chains show what the measurements seem to indicate, namely, that the conidia produced by the red-brown race R are somewhat narrower in proportion to their length than those of race G There is not enough difference to take either race out of Elliott's *A tenuis* group The spores of Roberts' saltants A and B show a much greater difference and his races are positively known to have arisen from a mycelium originally derived from a single spore

It is interesting to note that spore measurements of our races of *Alternaria* compare very well with those of Roberts' *A mali* and that some of the conidia have verrucose walls It is an old custom among farmers to store apples in the cellar for winter use and it may well be that, in this way, the particular cellar in which our patient contracted such severe attacks of asthma had become contaminated with *Alternaria mali* or with a race closely related to it As soon as the opportunity offers, tests will be made to determine whether our races G and R show any difference in their ability to bring on asthma



A B C D conidiophores and developing conidia of race R *G H I* the same for race G *E* a complete chain of conidia of race R *J* the same for race G *F* a rough wall conidium of race R All drawings were made to the scale indicated with the aid of a camera lucida

COMMENT

The observations previously made by Cadham, van Leeuwen and Hansen, and those here described offer an explanation of the activity of dust in producing asthma

As to the relationship of mold sensitiveness to the eczema in our patient, we have no conclusive evidence We know only that he gave a skin reaction to the mold frequently recovered from his skin lesions It is interesting, however, to note that Hilgermann [11] and

---

[11] Hilgermann R. Munchen med Wchnschr 68:702 (June 10) 1921

Niethe[12] attributed certain cases of eczema to sensitization to common molds

SUMMARY

In the case of asthma reported here, the attacks occurred in locations in which mold spores were abundant The patient showed extreme skin sensitiveness to a strain of *Alternaria* recovered from a house in which he had attacks Attacks were induced in this patient by the extract of *Alternaria* in powdered form and also by the broth in which it had been grown An attack was also induced by the dry powder of one of the *Circinella* isolated from another room in which he had attacks He did not give any marked skin reaction to an extract of the latter fungus

One Hundred and Sixty-Eighth Street and Broadway

CHRONIC ULCERATIVE COLITIS *

M H STREICHER, M D
AND
BERTHA KAPLAN, M S
CHICAGO

Until recently, all reports on the subject of ulcerative colitis were discouraging For many years it has been the opinion of most gastro-enterologists that the treatment of colitis was mainly that of the specific forms of ulcerative colitis and that the diagnosis of the nonspecific ulcerative colitis was based on the existence of colon ulcers with negative bacteriologic observations

The first suggestion that the so-called nonspecific colitis was an infectious disease was made by Bargen[1] in 1924 He maintained that a diplostreptococcus of definite morphologic and cultural properties is an important etiologic factor in the causation of certain cases of chronic ulcerative colitis Since then many investigators have confirmed his observations The European investigators, too, until of recent date have always looked on chronic ulcerative colitis as of nonspecific origin It is important to remember in this connection that distant foci of infection parallel to a great extent the infection existing in the colon

METHOD OF PROCEDURE

In the past three years we have carried on a careful survey of all cases of diarrhea observed in our gastro-intestinal clinic, first, to confirm or refute the observations of Bargen and, secondly, to determine the specificity and therapeutic value of autogenous vaccine The patients were properly prepared a day before and routine proctoscopic examinations were made in each patient In the years 1926-1929 about 1,200 proctoscopic examinations were made of which only sixty-five conformed to a clinical and pathologic picture of a chronic ulcerative colitis These sixty-five cases presented definite proctoscopic manifestations of an infectious process with ulcerations in various portions of the colon Cultures were then obtained through the proctoscope by means of a sterile swab and transferred at once to a proper medium for incubation and subsequent culture and subculture The cultures were inoculated in dextrose sheep s brain broth, on blood agar plates and in Endo's medium At the same time slides were prepared for Gram and acid-fast stains Whenever necessary sterile saline washings were made from the ulcers for guinea-pig inoculation Subcultures were made from dextrose brain broth as well as from the blood agar plates until pure cultures of the various organisms were obtained Cultures of green-producing gram-positive diplococci and other organisms were passed through the necessary sugars The individual strains of bacteria were then isolated from the cultures and a polyvalent vaccine was prepared The autogenous vaccine was then administered hypodermically to the patients in progressively increasing dosages in accordance with the severity of the infection Subcultures of chromogens were inoculated on plain agar and grown at room and incubator temperatures Rabbits were inoculated intravenously with from 5 to 7 cc of pure forty-eight hour dextrose broth cultures of green-producing diplococci, hemolytic streptococci and *Bacillus pyocyaneus,* respectively These rabbits were under careful observation

Table 1—*Summary of Sixty-Five Cases of Chronic Ulcerative Colitis*

Before Vaccine Therapy

Number of Cases	Per Cent	Average Number of Stools Daily	Average Weight Loss	Duration	Proctoscopic Observations	Age Variation
52	80	5 to 20	12 to 50 lbs	1 to 2 yrs	Stage of ulceration no Streptococcus hemolyticus present	18 to 57 yrs
5	8	6 to 30	40 lbs	4 yrs	Stage of ulceration Streptococcus hemolyticus present	30 to 75 yrs
8	12	40	60 lbs	8 yrs	State of ulceration superimposed infection	28 to 50 yrs

After Vaccine Therapy

Number of Cases	Per Cent	Average Number of Stools	Average Weight Gain	Number of Vaccine Injections	Proctoscopic Observations	Follow Up	Progress and Comment
52	80	1 to 3	8 to 10 lbs	25 to 75	Stage of inflammation	2½ yrs	Patients free of symptoms
5	8	2 to 10	5 lb	25 to 75	Stage of ulceration	3 yrs	Symptoms still present in mild form
8	12	12 to 30	Continued to lose	25 to 100	Stage of bleeding	6 mo to 1 yr	3 patients died 3 refused injections 2 worse with injections

RESULTS

Briefly summarized, the results in table 1 clearly demonstrate that most remarkable improvement was noted in about 80 per cent of the cases observed It must be noted in this connection that fifty-two patients in this group were free from a *Streptococcus hemolyticus* strain It is evident from the progress of the five patients listed in table 1 that the symptoms persisted after vaccine therapy The *Streptococcus hemolyticus* strain was present and remained present on reexamination with the proctoscope after injections of vaccine In this group of five cases the ulcers of the colon did not heal readily and showed little indication of tissue reaction The group of eight cases constitutes a large percentage of our failures Of the three deaths, two followed surgical operations while the third was apparently due to exhaustion and repeated bleeding spells

---

[12] Niethe Arch f Dermat u Syph **153** 358 1920

* From the Research and Educational Hospital Department of Medicine University of Illinois College of Medicine and the Grant Hospital

* The bacteriologic aspects of this problem including the preparation of vaccines were done by Miss Kaplan the clinical phases including proctoscopic examinations have been studied by M H Streicher

[1] Bargen J A Studies on Chronic Ulcerative Colitis J A M A. **83** 332 336 (Aug 2) 1924 Experimental Studies on Etiology of Chronic Ulcerative Colitis Collected Papers of the Mayo Clinic **16:** 241 245 1924 Experimental Studies on the Etiology of Chronic Ulcerative Colitis Suggestion for a More Rational Form of Treatment ibid **17** 7 66 276 1925 Chronic Ulcerative Colitis ibid **19** 351 362 1927 Treatment of Chronic Ulcerative Colitis Minnesota Med **10** 689 (Nov) 1927

Our results show that in most cases of ulcerative colitis green-producing gram-positive diplococci are found predominating Frequently these are in association with other bacterial flora The green streptococci fall into five groups according to their production of acid in carbohydrate mediums

TABLE 2—*Sugar Reaction Produced by the Gram-Positive Green-Producing Diplococci of Ulcerative Colitis*

	Sixty Five Cases of Ulcerative Colitis * 57 Strains		Thirty Four Cases of Other Diseases 23 Strains		Twenty Nine Normal Persons 9 Strains	
Lactose	56+	1—	23+	0	9+	0
Maltose	55+	2—	20+	3—	7+	2—
Mannite	17+	40—	7+	16—	4+	5—
Salicin	42+	15—	15+	8—	7+	2—
Inulin	0	57—	0	23—	0	9—

* In five cases of the sixty five hemolytic streptococci were present In seven cases of the sixty five spirilla predominated in smears In one case tuberculosis was found Among other diseases studied were mucous colitis chemical colitis amebic dysentery duodenal ulcer syphilitic obstructions and hernias

Tables 2 and 3 demonstrate the sugar reactions of the gram-positive green-producing diplococci of ulcerative colitis

In addition to the green-producing gram-positive diplococci and hemolytic streptococci we found other bacteria in ulcerative colitis such as diphtheroid bacilli *Staphylococcus albus* and *aureus*, *Staphylococcus albus-hemolyticus*, *Bacillus pyocyaneus*, *B lactis-aerogenes* and *B coli* In the normal cases we have not been able to isolate hemolytic streptococci Occasionally in addition to *B coli* we isolated green-producing gram-positive diplococci similar to those of ulcerative colitis, also *Staphylococcus albus* and *aureus*, *Staphylococcus albus-hemolyticus* *B welchii* and diphtheroid bacilli In three cases, spirilla predominated in the smears The green-producing gram-positive diplococci from all other conditions fall into five similar groups (table 3) Cases of ulcerative colitis which showed the predominance of spirilla in direct smears from the ulcers showed occasional green diplococci Rabbits which were inoculated with hemolytic streptococci showed lesions similar to those produced by the green diplococci The rabbits were inoculated intravenously with from 5 to 7 cc of a pure forty-eight hour dextrose broth culture of the organisms and allowed to live under observation The animals lived from twenty-eight days to five months after inoculation On autopsy the majority of animals showed severe congestion of the blood vessels, marked hyperemia and edema of the mucosa of the colon (nine of thirty-nine rabbits) In one autopsy the green diplococci were isolated from the ulcers of the colon of the rabbit Of the two rabbits inoculated intravenously with the pure culture of hemolytic streptococci (dextrose broth), the autopsy of one showed congestion, hyperemia and edema while that of the other showed ulcers of the colon from which hemolytic streptococci were isolated

TREATMENT

The method of approach in general was threefold, namely, prophylactic, dietary and specific We cannot overemphasize the extreme importance of proper rest in these cases, the necessity of removing all mental strain and the eradication of distant foci of infection In reference to diet, one is impressed considerably with the encouraging results obtained with an essentially high calory high vitamin and low residue diet It is true, however, that many clinicians recommend no special diet or a so-called general diet and allow their patients to adapt themselves to a suitable regimen This specific treatment consists of injections of polyvalent autogenous vaccine hypodermically The individual dosages vary from 0 1 cc to 1 5 cc depending on the extent of the process The proctoscopic examinations are repeated when needed and bacteriologic observations noted The patients remain under observation until free from symptoms and until proctoscopic examinations are negative bacteriologically and pathologically We wish to emphasize that no local treatment was administered and no irrigations were employed

COMMENT

If we assume from our bacteriologic observations that chronic ulcerative colitis is an infectious disease then the rationale of the specific treatment lies in active immunization against the causative organisms The causative organism in our opinion is not a single type of bacteria but a number of different types of bacteria or a number of different strains of the same bacterium, so that we are not justified in assuming that a green-producing gram-positive diplostreptococcus is solely responsible for the disease, because in 7 6 per cent of our cases hemolytic streptococci predominated Again, cases of ulcerative colitis in which injections are made with the vaccine from a pure culture of a green diplococcus show little or no progress, whereas the same cases treated with a polyvalent autogenous vaccine give encouraging results Many physicians believe that the autogenous vaccine has the properties of nonspecific protein therapy That this is not true is clearly demonstrated by the fact that negative results are obtained when typhoid vaccine or milk injections are substituted in these cases

One necessarily encounters the question of remissions or recurrences in ulcerative colitis If we assume that the autogenous vaccine therapy is specific or is actively immunizing the patients we should not expect the symptoms to recur In this series of cases 80 per cent of the patients had no remission for two and one-half years, it is true however that recurrences were frequent in thirteen cases and that the only logical explanation one can offer is that the mental makeup of these individuals was adverse and that these cases comprise a group in which there was considerable neglect and mismanagement We are of the opinion that recurrences are common in patients who have been neglected for several years and have not been on any systematic regimen in these cases it is most uncommon to observe any tissue reaction as a response to vaccine therapy In our experience recurrences are not frequent in cases that have been diagnosed early and properly cared for

TABLE 3—*Classification of the Fifty Seven Strains of Green-Producing Gram-Positive Diplococci According to Acid Production*

Sugars Used					Number of Strains
Lactose +	Maltose +	Mannite +	Salicin +	Inulin —	17
Lactose +	Maltose +	Mannite —	Salicin +	Inulin —	21
Lactose +	Maltose +	Mannite —	Salicin —	Inulin —	13
Lactose +	Maltose —	Mannite —	Salicin —	Inulin —	[illegible]
Lactose —	Maltose +	Mannite —	Salicin +	Inulin —	1

At this time we are not inclined to stress "the Bargen bacillus" as the primary etiologic factor of ulcerative colitis We are indebted considerably to Bargen for being the first to bring forth the idea that the so-called nonspecific chronic ulcerative colitis should be considered an infectious process

CONCLUSIONS

1 Chronic ulcerative colitis should be considered an infectious process

2 The green-producing gram-positive diplostreptococcus is not the sole etiologic factor of chronic ulcerative colitis

3 A polyvalent autogenous vaccine given hypodermically is of considerable therapeutic value

4 The green-producing gram-positive diplococci are all inulin negative and the majority are mannite negative

5 Similar green-producing organisms are found in amebic dysentery, duodenal ulcer, syphilitic obstruction, hernias, and in many other conditions, similar organisms are present in some normal cases

6 Hemolytic streptococci are also isolated from cases of ulcerative colitis

7 The green-producing gram-positive diplococci fall into five groups according to acid production in sugars

307 North Michigan Avenue

BENIGN LESIONS IN CARDIAC PORTIONS OF ESOPHAGUS AND STOMACH

ROENTGENOLOGIC DIAGNOSIS *

ALEXANDER B MOORE, M D
ROCHESTER, MINN

The cardiac segments of the esophagus and stomach constitute a rather unsatisfactory field for roentgenologic diagnosis Lesions encountered in this area are relatively fewer and, with certain exceptions, more difficult to demonstrate than those which affect the distal portion of the stomach or the duodenum Neither the esophagus nor the upper part of the stomach is accessible to the manipulation which is of such valuable aid in examining other parts of the alimentary canal, and the technic employed as a routine for examination of the digestive tract must often be supplemented by special procedures to elicit signs of disease Technical minutiae are irksome to the examiner, but unless he employs them and exercises punctilious care small lesions are likely to escape discovery

Benign lesions in this field comprise chiefly cicatricial strictures, cardiospasm, diverticula, nonmalignant new growths, ulcers and diaphragmatic hernias

Cicatricial stricture is commonly a result of drinking caustic liquids, such as lye or acids, but it may follow vomiting of pregnancy or typhoid ulceration and occasionally it ensues from any of a variety of diseases and injuries Strictures from caustics are usually situated in the upper third of the esophagus, whereas those due to other causes are likely to be found in the lower third Often the strictures are multiple, but they may be single In the majority of cases the roentgenologic manifestations are rather typical Immediately above the stenosis the barium mixture forms an inverted cone and trickles through the constriction in a fairly direct line, although at intervals the linear shadow may have unilateral or fusiform expansion at points where the contraction is less pronounced Obviously, the picture may resemble that of cardiospasm or cancer However, cardiospasm is almost invariably situated precisely at the hiatus in the diaphragm or at the cardiac opening, and dilatation tends to be extreme, cicatricial strictures in the lower third seldom coincide with the points mentioned, and the dilatation is rarely as great as that of cardiospasm In cancer, as a rule, the barium shadow above the stenosis is not smoothly conical but irregular, and the constricted channel below is markedly tortuous There is little reason to confound cicatricial stricture or stenosis from any intrinsic disease of the esophagus with compression stenosis from cardiac enlargement, aortic aneurysm or mediastinal tumor Narrowing by compression is not extreme, is smoothly regular and affects a considerable extent of the gullet, and its cause should be apparent

Among demonstrable nonmalignant conditions of the distal portion of the esophagus, cardiospasm is most common In a majority of cases the barium shadow terminates in an evenly rounded, symmetrical cone, in a minority the stenosis is at the cardiac aperture and the epicardia is depicted as a nipple-like prolongation of the shadow Exceptionally the stenosis is slightly above the hiatus Dilatation proximal to the spastic contraction is usually much greater than that incident to other obstructive conditions, and is sometimes prodigious Usually the flaccid walls exhibit little if any peristaltic activity, but occasionally vigorous waves of contraction or reverse peristaltic movements are observed Frequently the esophagus is not only dilated but elongated, and pursues a winding course or is partially folded in its lower extent I have encountered instances also in which the redundant esophageal sac had prolapsed through the diaphragm and invaginated into the upper segment of the stomach, the epicardia being bulbous and sharply demarcated from the main portion of the esophagus at the hiatus

So striking and characteristic is the appearance of cardiospasm that the diagnosis will not often go astray Dilatation of the esophagus resulting from a high-seated hour-glass constriction of the stomach has only a superficial resemblance to cardiospastic dilatation, and its nature is obvious When the esophagus is elongated and folded below, the pouch might be mistaken for a low diverticulum Rarely, bits of food retained in the esophagus deform the terminal shadow and imitate the defects produced by cancer, or, with equal rarity, the barium shadow above an obstructing cancer ends in a smooth cone like that of cardiospasm If the spastic stenosis is above the hiatus the condition can be confounded with cicatricial stricture, and vice versa Notwithstanding these sources of error, the enormous dilatation will usually distinguish cardiospasm from any simulant For a considerable time after dilatation of a cardiospasm with the hydrostatic bag or sounds, the barium mixture will lag to a certain degree at the site of stenosis, and this fact alone does not warrant the conclusion that the treatment has been ineffective

A few examiners have reported the observation of transitory spasm at the cardia or in other parts of the esophagus, either momentary or lasting twenty or thirty seconds I have not seen any constrictions of this kind worthy to be dignified by the name of spasm, although occasionally I have noted exaggerated, dis-orderly or hesitating peristaltic contractions which I thought could be attributed to the patient's agitation or his repugnance for the barium mixture

---

* From the Section on Roentgenology the Mayo Clinic

* Read before the joint meeting of the Section on Gastro-Enterology and Proctology and the Section on Radiology at the Eightieth Annual Session of the American Medical Association Portland Ore July 11 1929

Diverticula are extremely rare at the lower end of the esophagus When they occur here, they are usually situated on the anterior wall and project to the left As a rule, they are small and finger-like, and their appearance is distinctive, if they are large, they may be imitated by partial herniation of the stomach through the hiatus, or by the sacculated folding which sometimes results from cardiospasm with elongation of the esophagus Rarely, a low diverticulum coexists with cardiospasm

Diverticula in the upper third of the stomach are not altogether uncommon They are usually single and arise from either curvature or the anterior or posterior wall In the tangential view, a diverticulum appears as a rather slender pendulous sac, communicating at its upper end with the gastric lumen, which is otherwise normal It is to be distinguished from the pseudodiverticulum or accessory pocket of a perforated ulcer which is most often rounded or irregular, may exhibit a fluid level with an air bubble above and is likely to be associated with hour-glass contraction of the stomach in the plane of the pocket or with other spastic manifestations Ordinarily, single or multiple diverticula of the bowel, without any complicating inflammation, do not have clinical significance but a considerable proportion of the gastric diverticula operated on at the Mayo Clinic have been found to contain cancerous tissue at the tip

Although syphilis of the esophagus, in the form of gumma or stricture, has an established but minor place in the literature, it is uncommon, and I cannot cite a case from experience At the clinic all cases in which the condition was suspected of being syphilitic because an obstructive esophageal lesion and a positive reaction to the Wassermann test were associated proved later to be cancer

Gastric syphilis is far less rare, and in numerous cases of a series which I have previously reported the cardiac segment was implicated It is noteworthy, nevertheless, that apparently the cardia is involved only by extension from the lower segments, and its uppermost portion, enclosing the gas bubble, is usually intact This fact, in conjunction with regular, concentric narrowing of the remainder of the stomach or contraction of the middle segment in the form of a dumb-bell, aids in the diagnosis

Benign new growths of the esophagus are to be rated among the pathologic curiosities, and I can recall only two cases that have come under my immediate observation In the first case, the tumor, a hemangioma several centimeters in length, was suspended from its point of attachment in the middle third of the esophagus It produced a central translucent area in the barium shadow, and as this is characteristic of benign tumors in other parts of the alimentary canal the diagnosis was made accordingly In the second case multiple small polyps in the lower half of the esophagus caused obstruction and filling defects, but these signs were wrongly attributed to cancer

Benign tumors in the stomach are more likely to be found in its distal two thirds, but they arise occasionally in the cardiac portion In one case the new growth was sessile and was on the posterior wall just below the plane of the esophageal opening It caused the entering barium stream to divide but otherwise would not have been discovered, for the gastric shadow was normal after complete filling In another case the tumor was similarly situated but was pedunculated it not only split the barium stream but produced the characteristic central defect in the shadow of the filled stomach and could be moved about by manipulating the stomach below

Observers have reported instances of peptic ulcer in the lower segment of the esophagus which in their morbid anatomy were entirely comparable to chronic gastric or duodenal ulcers Because of the constricting spasm which they tend to produce their roentgenologic manifestations were often described as similar to those of cardiospasm, but in at least one recorded case the ulcer had perforated the esophageal wall and formed an accessory pocket Experience in the clinic has been confined to single or multiple, large or small superficial erosions which are often incident to cardiospasm or the result of trauma, they have no resemblance to chronic peptic ulcer morphologically, and are not discernible roentgenologically

It is well known that the site of election of gastric ulcers is in the middle third of the stomach in the vicinity of the angular incisura Occasionally however, they are situated in the cardiac third Most often the ulcer is on or is sufficiently near the lesser curvature to produce the usual marginal niche Rarely the niche is well out on the posterior or anterior wall where it is visible only as a shadow fleck and, when small is hard to discover I have never seen an ulcer above the level of the esophageal opening, that is to say, in the area of the gas bubble

Of particular interest among the abnormalities to which this region is subject is herniation of the stomach through the diaphragm, for its roentgenologic features are varied and sometimes spectacular It is often mistaken for other conditions, and it often passes undiscovered Hernia through the hiatus is usually congenital and associated with a short esophagus Before the barium is given the gastric gas bubble may be visible above the diaphragm and behind the heart As the barium descends, it is inclined to lag in the lower part of the esophagus and then enters the cardia which is obviously above the diaphragmatic arch The herniated portion of the stomach, which of course varies in size may surround the apparently invaginated lower end of the esophagus symmetrically, or it may project toward either side, more often toward the left Occasionally a gastric ulcer with a manifest niche is seen at the level of the constriction produced by the hiatus Below the diaphragm the stomach is diminished in size in proportion to the extent of herniation above, and the pyloric end may be drawn over to the median line or to the left of the spine The shadow of the diaphragmatic arch is distinguishable, and it moves normally on respiration

Traumatic hernias through the diaphragm are almost invariably on the left side and the rupture may occur at any point, centrally, mesially or laterally As a rule, the barium passes without delay through the esophagus, although the latter may be unduly curved or angled in its course Deformity of the gastric shadow varies in character and degree and is partly dependent on the extent of herniation into the thoracic cavity The diaphragm is fixed, its shadow is hard to trace, but a remnant of the arch can usually be discerned

Errors in the diagnosis of diaphragmatic hernia are easily made In the congenital type with a short esophagus, the examiner may think of cardiospasm or of low diverticulum If the niche of an ulcer is apparent, he may conclude that the picture is simply that of gastric ulcer with hour-glass deformity Occasionally, the gastric deformity produced by hernia, whether congenital or acquired, is misinterpreted as cancer, but this error is hardly to be condoned Fundamentally, the diagnosis of hernia of the stomach rests on ascertaining the fact that at least a portion of the stomach is above the diaphragm An unusually high position of the stomach is not diagnostic, for this occurs also in diaphragmatic eventration However, in eventration the shadow of an intact arch can be traced in most instances, and its respiratory excursions are reversed from the normal It is my impression that true diaphragmatic eventration is extremely rare, and that an abnormally high gas bubble usually signifies diaphragmatic hernia On the other hand, the arched shadow of the cardiac dome in a case of hernia may be mistaken for that of the diaphragm, thus causing a negative error It should be unnecessary to say, also, that when the patient stands, a hernia may be spontaneously reduced, or it may not be possible to demonstrate the herniated portion of the stomach Accordingly to establish the diagnosis or to exhibit the gastric contours adequately, it is often necessary to examine the patient in the supine, prone or Trendelenburg position Since the colon is often implicated in the hernia, examination with a radiopaque enema is desirable to confirm or amplify the diagnosis I would especially emphasize the opinion that any abnormality of the barium inflow at the cardia, without definite obstruction, should be regarded as suggestive of congenital hernia and a stimulus to thorough investigation

Finally, even at the risk of being trite, I would point out again that the intimate cooperation of roentgenologist and clinician, which can seldom be omitted with safety whenever they are both concerned, is indispensable in this particular field Although exercised to best advantage in separate hands, the roentgenologic, clinical, esophagoscopic and gastroscopic examinations are not really independent but complementary and mutually corrective

ABSTRACT OF DISCUSSION

Dr R R. Newell San Francisco Dr Moore showed an ulcer of the stomach higher than I have ever seen one It is certainly unusual to find an ulceration of the stomach in the upper quarter Rare as diverticula of the stomach are, I believe they are more frequent in the upper portion than are ulcers in the upper portion It is not remarkable that dilatation of the esophagus in a case of cardiospasm is apt to be so much greater than it is above a carcinoma We know that cardiospasm is ordinarily a much more chronic disease and has often existed for ten years or more at the time the roentgenologist sees it, and the great dilatation is due to the great length of time available for stretching the esophagus It does us good once in a while to stop to think how peculiarly fortunate we are today to have the x-rays for the diagnosis of these diseases in the middle of the body where they cannot be discovered with the eyes or with the fingers As far as I know the first case of cardiospasm was reported more than a hundred years ago, and it is interesting to read this old English physician's explanation of how he investigated the man's difficulty in swallowing by passing a 'large, blunt instrument' down the poor fellow's esophagus He shoved and shoved and finally shoved the blunt end through the cardia into the stomach, and then he couldn't get it back again So having shoved hard he then pulled and pulled and pulled and finally succeeded in getting it out again, 'with such a loud noise that it frightened the bystanders ' I was impressed by what Dr Moore had to say about one's ability to help himself in diagnosis by palpation It is true that palpation is a tremendous help especially in regard to the duodenum In the lower end of the esophagus we have only gravity to help us in the manipulation Dr Hickey pointed out the advantages of using both thick and thin meals and placing the patient in various more or less unusual positions, so as to get the barium to go into all the corners We must use every possible arrangement of patient and x-ray beam if we are to avoid missing the less obvious lesions in this region

Dr Frank Smithies Chicago I am glad that Dr Moore emphasized the fact that in this lesion there is diffuse dilatation practically of the entire esophagus The dilatation varies in extent but it is always present, thus differing definitely from the esophageal contour associated with ulcer or cancer The name cardiospasm should not be used alone It would be preferable always to speak of cardiospasm and diffuse dilatation of the esophagus, otherwise confusion exists in the minds of the general practitioner, and even of the specialist Cardiospasm is not the same as spasm at the cardia Cardiospasm is accompanied by anatomic change in esophageal structure It is precipitated by causes unknown to us In association with this lesion, there are definite evidences of faulty innervation of the diaphragm and the lower esophagus In the treatment of this ailment one cannot rely on Christian science or the spine punching of the osteopaths or the chiropractors, one must apply measures which actually treat an organic lesion and not expect a special kind of diet and belladonna or some bromide to relieve the disability Symptomatically in the organic lesion of the esophagus associated with stricture, the patient begins gradually to abstain from taking solid food usually when he comes for examination he has been eating purees, and then water and milk In cardiospasm, from the beginning, the individual handles solid foods fairly well, but if he takes a glass of water or a cup of soup at the beginning of the meal he has to leave the table hurriedly and find the kitchen sink This is a valuable point of differentiation between cardiospasm and the organic stricture of the esophagus I have seen a number of instances of injury or perforation of the esophagus because an unguided bougie has been introduced either as explorative or in therapy Certainly if an unguided bougie is passed it should be done before the fluoroscope, but I feel that all bougies should be passed on a silk thread guide, so that one knows that all the time it is in the lumen of the esophagus and hence will not injure the esophagus or the stomach The apparatus for dilation of the cardia devised by Henry Plummer is excellent Its limitation is that it requires a water attachment I have devised an apparatus of a pneumatic type which has all the advantages of Plummer's dilator and in addition certain practical improvements I have used this apparatus for more than a year and have found its results to equal those obtained with Plummer's apparatus

Dr Zachary Sagal, New York From the clinical standpoint the diagnosis of cardiospasm, when it is typical and of long standing, is very simple However, those cases which have not existed long and are due to some other pathologic condition, such as ulcerations, present considerable difficulties and these difficulties are multipled by the fact that patients will either not give sufficient information or deliberately misguide the physician, fearing that they may prejudice him one way or the other A patient was referred to me for observation He had asked his physician not to give me any information, and himself gave me a history of short duration The fluoroscope, however, revealed a typical cardiospasm, and twenty-four hours after the barium was given there was not a bit of barium in the stomach That emphasized the point brought out by Dr Hickey of the trickling of the barium through the lower end of the esophagus, which is typical of malignant growth Later we learned that a diagnosis of carcinoma had been made five years before and the man was urged to submit to operation immediately, but the condition promptly subsided. A diagnosis of cardiospasm was made roentgenologically and an esophago scopic examination revealed an ulcer at the cardia

Dr F A Speik, Los Angeles I am a disciple of Sippy He was the first to devise an air bag in contrast to the Plummer bag I have had only eighteen cases of cardiospasm, but they have all been treated successfully with the Sippy bag As Dr Smithies says, the big point in diagnosis is this In carcinoma of the esophagus the patient has difficulty in swallowing solids but not so much [illegible] be dignified by the name of spasm, has a great [illegible]casionally I have noted exaggerated, dis-of the etiologic factors in the production of cardiospasm is drinking cold beverages Many people who have no cardiospasm at all may feel a tightness and stricture in the esophagus and chest after a cold drink. Jackson, however, does not believe that it is due entirely to a spasm of the cardia or of the esophagus but to a spasm of the diaphragm. He speaks of this opening in the diaphragm as a pinch-cock which goes into spasms and causes a retrograde regurgitation. I recall the case of a woman who had been operated on for a stricture of the pylorus She was vomiting food and had all the evidences of a stricture of the pylorus A gastro enterostomy was done, but the patient did not improve, so she came to Chicago to see Sippy An assistant made the diagnosis because the patient had great difficulty in swallowing liquids She was in an emaciated condition and died soon afterward Dr Sippy had this pathologic specimen which showed that the fusiform sac held as much as a quart of liquid It folded up like a tobacco pouch. The musculature was hypertrophied and the mucous membrane was in folds

Dr John H Fitzgibbon, Portland, Ore It may be somewhat aside from Dr Moore's paper to discuss the treatment of cardiospasm, but as treatment has been mentioned in the discussion, it will perhaps not be out of place to describe a modification of the Sippy air bag dilator which I have developed recently For a number of years, I used the Sippy air bag dilator with satisfactory results except in cases in which the esophagus was markedly dilated In attempting to dilate in a case in which there was a great deal of dilatation and sacculation of the esophagus with increased angulation above the hiatus, I discovered, by fluoroscopy that my difficulty in getting a satisfactory stretching was due to the fact that the pressure exerted by air entering the bag caused it to slip upward into the esophagus without properly stretching the cardia The great size of the esophagus above permitted lateral bending of the shaft of the instrument, so that the bag could not be held in proper position while being inflated To remedy this, I first tried a saddle-shaped bag and later an elongated bag but without much improvement Obviously the reason the bag tended to slip upward was that it was inflated from above Had it been inflated from the stomach side it would have slipped downward With this idea in mind we built a bag which is inflated from the two ends at the same time, so that the pressure is equal above and below the diaphragm To accomplish this, it was merely necessary to run a small tube down inside the bag, so that air could enter the two ends simultaneously This instrument cannot slip, and has been used many times with excellent results. The same principle may be applied to either air or hydrostatic dilators if desired The original Sippy cardiospasm dilator was satisfactory in most cases, but the modification has definitely improved our results, particularly in patients with more than average dilatation of the esophagus above the stenosis

Dr Clarence G Toland, Los Angeles I am not a roentgenologist, but I am much interested in the x-rays I endeavor to practice surgery The progress and development of roentgen diagnosis, especially in relation to surgery, is interesting I have listened with the greatest of interest to all the papers You roentgenologists have made better surgeons of us because it is just as important that we who are practicing surgery should come into the x-ray laboratory to watch what you are doing as it is for you to follow your cases into the operating room If we could have better cooperation between the departments, our patients would be greatly benefited You tell us exactly what to do and how to do it If we surgeons would only listen to your teachings we would save a great amount of suffering in cases of acute bowel obstruction

Dr. Tate Miller, Dallas Texas The cause of cardiospasm is not known. One hesitates to mention foci of infection in connection with this condition, however, I have had two cases in the last ten years that have resisted the usual treatment with the Plummer instrument. I must state, however that because of an occasional catastrophe when the Plummer instrument is used at high pressure, I was afraid to run up the pressure in the treatment of these cases as high as is recommended, so that it is possible that in these cases dilation was insufficient. In one case with recurring symptoms the removal of some definitely infected tonsils, and in another case the removal of an appendix that may have been causing trouble all along but that we had failed to recognize prevented further returns of cardiospasm Both these cases had persisted in spite of the dilations until the operative measures were taken, so that I feel that whenever the cause of cardiospasm is found a focus of infection will be found to have some starting irritative causative activity

Dr. A B Moore, Rochester, Minn. Since there has been such unanimity of opinion in regard to the treatment of cardiospasm, it would seem that the diagnosis is the important factor I have seen several instances similar to the one which was quoted this morning, in which a case of cardiospasm with marked obstruction and diffuse dilatation had been treated for pyloric obstruction This seems to be an inexcusable error and yet it apparently is one which occurs quite frequently While I believe that the pain of cardiospasm is usually associated with the swallowing of liquids we see cases in which the discomfort is associated with the taking of solid food Not infrequently a case which roentgenologically shows no obstruction to the liquid suspension of barium will show a definite lagging and irritability of the lower third of the esophagus when a semisolid barium-impregnated meal is given While the pain of cardiospasm is usually suggestive, I have seen cases in which a previous diagnosis of angina had been made, when in reality the painful seizures were caused by an obstruction in the cardiac end of the esophagus

HERNIA OF THE STOMACH THROUGH THE ESOPHAGEAL ORIFICE OF THE DIAPHRAGM *

MAX RITVO M.D
BOSTON

An "esopnageal orifice hernia" as the term is used throughout this article, is a protrusion of a portion of the fundus of the stomach through the esophageal opening of the diaphragm into the thorax This condition was formerly considered very rare and of but slight clinical significance Thus, in 1911, Eppinger [1] summarized the literature on diaphragmatic hernia and reported that of 635 cases of herniation through various portions of the diaphragm, only eleven involved the esophageal hiatus Quenu in 1920 [2] found only one esophageal orifice hernia in a series of 116 cases which had come to operation Breitner [3] stated that, of the large number of diaphragmatic hernias reported up to 1921, only forty-four had been diagnosed during the life of the patient, and in only six of these was the diagnosis made without the aid of the x-rays These studies were carried out before the roentgen examination of the gastro-intestinal tract with the opaque meal had come into widespread use

During the past decade, numerous reports in the literature indicate that esophageal orifice hernias are much more common than was previously supposed In 1924, Carman and Fineman [4] reported seventeen cases, fifteen of which had been diagnosed roentgenographically during the years 1923 and 1924 Morrison [5] in 1925 stated that he had encountered forty-two cases of diaphragmatic hernia of the fundus of the stomach

been discovered, for the gastric shadow

---

* From the X Ray Department Boston City Hospital Dr P F Butler Roentgenologist in Chief

* Read before the Section on Radiology at the Eightieth Annual Session of the American Medical Association Portland, Ore July 12 1929

[1] Eppinger H Pathologie des Zwerchfels Supplement to Nothnagel s zu Spezielle Pathologie und Therapie Holder Wien und Leipzig 1911

[2] Quenu J Les hernies diaphragmatiques etude clinique et operatoire, Paris Arnette 1920

[3] Breitner B Zwerchfellhernien Arch f klin. Chir **117** 164 1921

[4] Carman R. D, and Fineman S Roentgenologic Diagnosis of Diaphragmatic Hernia. Radiology **3** 26 (July) 1924

[5] Morrison L. B Diaphragmatic Hernia of Fundus of Stomach Through the Esophageal Hiatus J A. M A. **84** 161 (Jan. 17) 1925

through the esophageal hiatus in 3,500 cases of gastric disease studied roentgenologically During the following year, his series [6] had increased to fifty-three In 1926, Pancoast and Boles [7] published reports of fifteen cases of nontraumatic, left diaphragmatic hernia Hedblom [8] found thirty-two cases of hernia through the esophageal orifice in 163 cases of diaphragmatic hernia, an incidence of more than 20 per cent Akerlund [9] reported thirty cases of hiatus hernia in 1926 and noted that in his review of the literature he had been able to find sixty cases My series comprises sixty cases of esophageal orifice hernia These occurred over a period of five years and were all diagnosed during the roentgen examination of the alimentary tract During this time, I have examined a total of about 8,000 gastro-intestinal cases with the barium sulphate meal

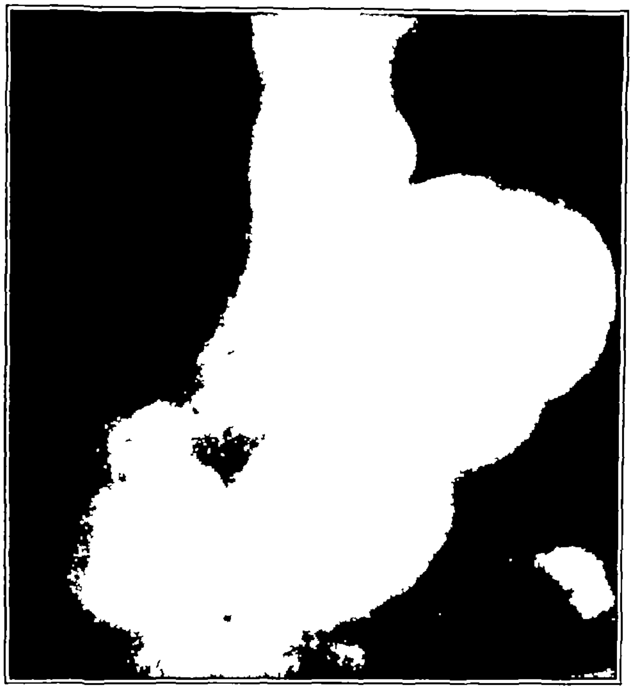


Fig 1—Esophageal orifice hernia. The herniated portion of the *stomach is completely filled with the opaque mixture* It lies above and to the right of the cardia overlapping the shadow of the spine The hernia connects directly with the cardia by a narrow isthmus at the esophageal opening of the diaphragm.

The apparent rarity of this lesion previous to the advent of the roentgen examination is not difficult to explain This type of hernia has neither a definite history nor typical signs, so that clinical diagnosis is extremely difficult As this lesion occurs in a situation very difficult of access surgically and in a region seldom explored during abdominal operations, the surgeon is not apt to discover the existence of the hernia At autopsy, the muscular relaxation and decreased intra-abdominal pressure make it easy to overlook the presence of this condition The roentgen examination is therefore the best method of revealing the hernia and is usually the only means of arriving at a diagnosis

ETIOLOGY AND PATHOLOGY

Enlargement of the esophageal hiatus of the diaphragm with resultant herniation of a portion of the cardia of the stomach into the thorax may be congenital or acquired The former type is subdivided into two groups (*a*) congenital maldevelopment of the diaphragm with improper fusion of its component parts and (*b*) delayed descent of the stomach If the former defect involves the region of the esophageal orifice, a hernia of the hiatus type results The stomach is a thoracic organ during early embryonic life After its migration into the abdomen, the various parts of the diaphragm meet and fuse, leaving a small opening for the esophagus If the stomach is delayed in its descent, the diaphragm at the time of fusion of its component parts finds the stomach instead of the much smaller esophagus lying *partially in the thorax and partially in* the abdomen This results in an enlargement of the esophageal hiatus The stomach usually completes its descent at a later period In very rare instances the shortening of the esophagus persists permanently, causing a condition known as thoracic stomach

The acquired type of esophageal orifice hernia *is due to increased intra-abdominal tension* This heightened tension may be caused by one or more of the following conditions marked constipation, pregnancy, severe, prolonged physical exertion, a blow on the abdomen, obesity, which increases the deposit of fat in the omentum, mesentery and subperitoneal tissues, enlargement of the prostate with consequent straining, *chronic cough, tight abdominal bands and ascites* In *addition to* these, there must in each instance exist some unknown condition which accounts for the herniation being through the esophageal orifice rather than at one of the more common sites of hernia A congenital weakness of the musculature of the diaphragm is probably the determining factor

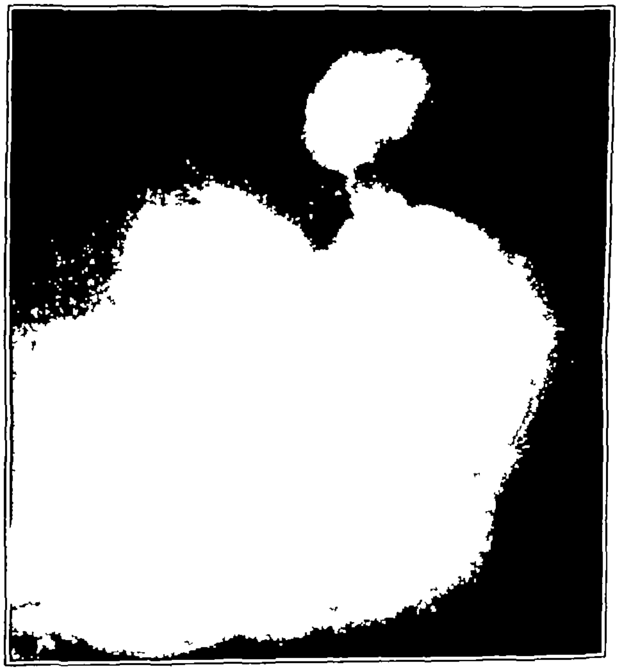


Fig 2—Esophageal orifice hernia The hernia is partially filled with the opaque mixture and also contains gas as evidenced *by the* area of increased radiance just above the left diaphragm

The degree of enlargement of the esophageal hiatus may vary widely Normally, the orifice admits one finger. In the cases of hernia, the opening may admit two fingers or at the other extreme be so large that the entire hand can pass through freely. The size of the hernia depends on the width of the aperture in the diaphragm, the degree of intra-abdominal tension, and the amount of fluid and gas in the stomach. The position of the patient is also important in this respect, as the hernia is most apt to reduce itself with the patient upright and is usually largest in the recumbent position.

---

[6] Healy T R Symptoms Observed in Fifty Three Cases of Nontraumatic, Diaphragmatic Hernia Am. J Roentgenol **13** 266 (March) 1925

[7] Pancoast H K and Boles R S Nontraumatic Left Diaphragmatic Hernia Radiology **3** 26 (July) 1924

[8] Hedblom C A Diaphragmatic Hernia J A M A **85** 947 (Sept 26) 1925

[9] Akerlund A. Diaphragmatic Hernia of the Esophageal Hiatus Acta Radiol **6** 3 *1926*

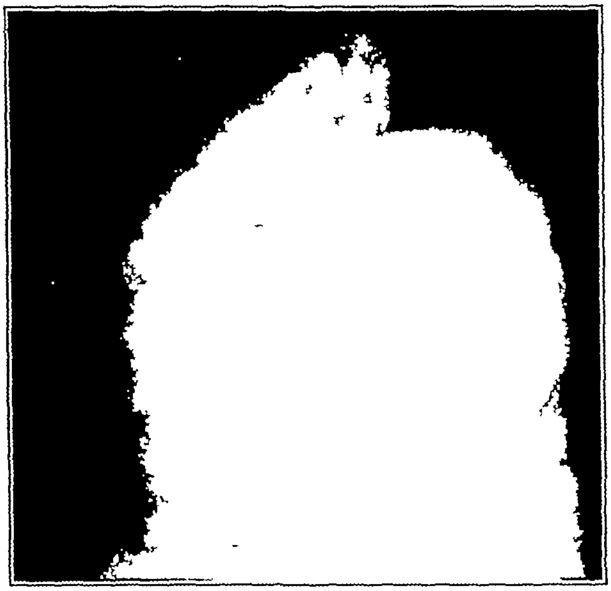


Fig 3.—Esophageal orifice hernia. The hernia contains only a small amount of the barium meal. The gastric rugae are well shown above the diaphragm overlying the shadow of the heart.

The smallest hernia was about the size of a walnut and the largest included the entire upper half of the stomach, with almost every possible variation between these extremes.

In the greater proportion of cases, the hernia was to the left of and behind the esophagus. Occasionally the herniated portion of the stomach partially encircled the esophagus. Very large hernias may displace the heart to the right. It is interesting to note that in the five year period during which my cases occurred, I found no hernia through either the aortic or the vena cava openings in the diaphragm. This is probably because herniations rarely if ever occur through these orifices. The aortic hiatus is an osseo-aponeurotic foramen formed by the tendinous arch of the diaphragm being thrown across the anterior portion of the bodies of the vertebrae from the crus on one side to that on the other, it is therefore really behind the diaphragm. The foramen for the vena cava is tendinous and roughly quadrilateral, and the highest of the diaphragmatic apertures. Because of their situation and structure these openings do not lend themselves to dilation.

The present series comprised forty-one women and nineteen men. The ages varied from 21 to 72 years. The distribution by decades was as follows: 21 to 30 years, four cases, 31 to 40, eight cases, 41 to 50, eighteen cases, 51 to 60, sixteen cases, and 61 to 72, fourteen cases.

Our clinic is composed almost entirely of adults, which is probably the reason for the youngest patient in this series being 21 years of age. Numerous cases are on record in very young people. The majority of the patients are in the "cancer age" and several were referred to the x-ray department with the clinical diagnosis of probable carcinoma of the stomach.

SYMPTOMS

In fourteen cases of this series, there were no symptoms which appeared to be due either directly or indirectly to the hernia. These patients were referred for roentgen examination with the following clinical diagnoses: intestinal obstruction, three cases, ascites five cases, appendicitis, three cases, pulmonary tuberculosis and tuberculous enterocolitis, three cases. The hernias were usually small, varying in size from a walnut to a plum, and were discovered during the routine roentgen studies of the gastro-intestinal tract. It appears probable that the hernias were present for long periods without causing ill effects. These patients may, of course, develop symptoms later. It is interesting to note that most of these cases presented those etiologic factors which were just enumerated as important in the causation of this type of hernia.

In the remaining forty-six patients, there were symptoms of varying severity but in each case sufficient to cause the patient to seek medical advice. In only three instances was there any other demonstrable pathologic change to which the complaints might have been ascribed. As a rule, the symptoms were mild or moderate, being severe in only six or seven cases. The duration was on the average from three to four years, the shortest being six months and the longest fifteen years. In none of the cases did the hernia cause a condition which could be classed as acutely surgical, requiring immediate operation. While incarceration and strangulation are theoretically possible these complications did not occur in any of our patients.

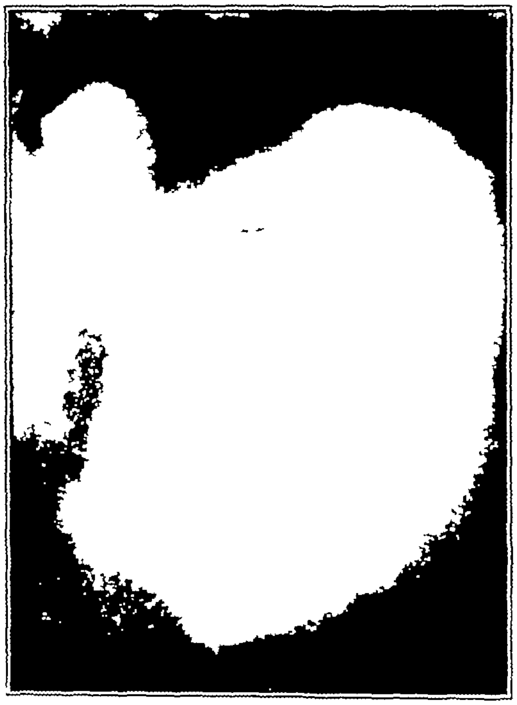


Fig 4.—Esophageal orifice hernia. The hernia is oval. Its connection with the cardia is well shown. The lower end of the esophagus is also filled with the opaque mixture and is partially encircled by the hernia.

The commonest complaint was pain in the epigastrium, which was present in thirty-one cases. The pain varied widely from a sensation of pressure to moderately severe colic. Most commonly it was described as a dull, heavy ache under the xiphoid Radiation was rarely present In four patients, this sensation "went through to the back" and in three others it radiated to the right and left The time of occurrence of the pain was very variable Most frequently, it came on during or soon after a meal In several, the first few mouthfuls of food caused distress In these patients, a hot drink or resting for a short while often gave relief In other instances, it was necessary to get up and walk about for a few moments, after which the remainder of the meal could be finished in comfort This was probably due to the fact that the herniated portion of the stomach became filled with the first swallows of food, causing the sensation of weight and pressure Following rest, the drinking of hot liquid or walking about, the hernia reduced itself and no further discomfort was experienced This is one of the most typical symptoms of this lesion and I have been able to diagnose the presence of a hernia clinically in several cases on the basis of this complaint In general, the pain was less apt to be present or was relieved more quickly if the patient was sitting or standing and was aggravated by the recumbent position In some instances, the distress was said to occur before eating and, in a few others, two or three hours after meals In five patients there was pain during the night Eleven stated that food increased the pain, in seven, food, sodium bicarbonate or a hot drink gave relief The remainder showed no reaction to the taking of food

Heartburn was present in twenty-six cases, gas and belching in twenty-two and nausea and vomiting in twenty-five and twenty, respectively In eight cases, vomiting, usually of small to moderate amounts, occurred during the course of the meal with complete relief thereafter, so that the remainder of the meal could be finished without discomfort The time of vomiting varied from a few minutes to several hours after eating Five patients noted blood in the vomitus This is believed to be due to the presence of small ulcerations in the herniated portion of the stomach Regurgitation was complained of in sixteen cases, most frequently in the morning soon after awakening Dysphagia was present in three cases and was doubtless caused by the pressure of the herniated portion of the stomach on the lower esophagus This symptom, although rare, is of great importance, as all of these patients were thought to have early carcinoma of the esophagus clinically Constipation was an outstanding complaint, being present in thirty-two cases This gives a percentage of more than 50 in our series, which is a higher incidence than in a group of unselected patients of the same age periods The straining at stool incident to the constipation is doubtless a factor in causing the hernia

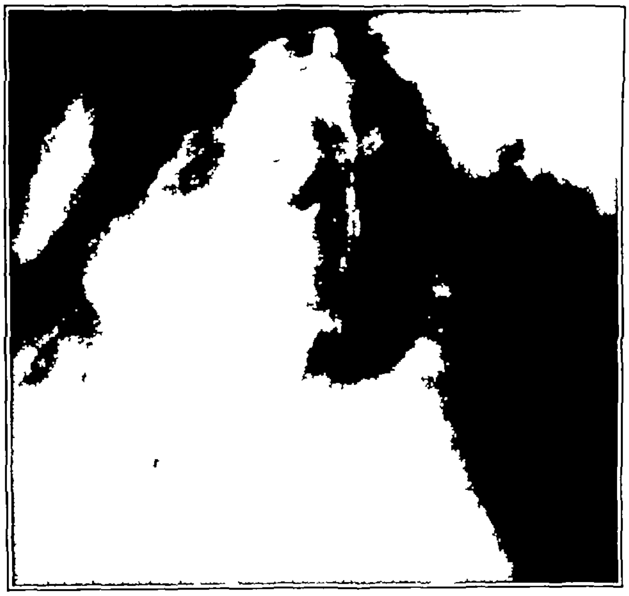


Fig 5 —Esophageal orifice hernia Lateral view of the chest showing the esophagus partially filled with the opaque mixture and the hernia lying just above the diaphragm The hernia is anterior to the lower part of the esophagus in this instance

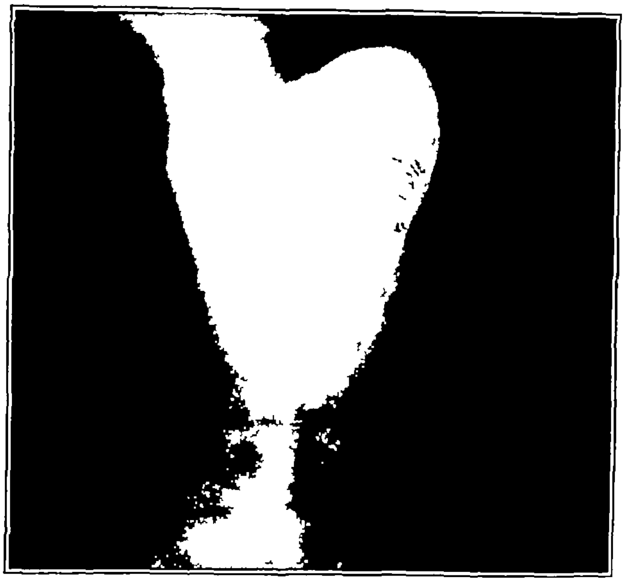


Fig 6 —Eventration The left side of the diaphragm and the stomach are markedly elevated. Attention is called to the relation of the esophagus to the stomach Fluoroscopic observations demonstrated that there was no herniation the stomach lying entirely below the diaphragm

Seven of the patients in this series had one or more abdominal operations without relief Several others had been advised to have operations with various clinical diagnoses Three patients had had the gallbladder removed and two the appendix One patient had an exploratory laparatomy and was informed that no pathologic condition had been found The seventh of this group had been operated on three times within the past five years, first, for the removal of a "chronic appendix," then for a cholecystectomy, and finally for adhesions She presented a hernia the size of a plum which had probably been the cause of her symptoms, as her complaints were the same after the operations as before Five patients had previously been studied roentgenographically and informed that there was no pathologic process in the gastro-intestinal tract

PHYSICAL SIGNS

Small or medium sized hernias give no physical signs Large hernias simulate pneumothorax or hydrothorax in rare instances Splashing, gurgling and similar sounds may occasionally be heard over the lower portion of the left chest

ROENTGEN OBSERVATIONS

Roentgen study is of the utmost importance in esophageal orifice hernia because it usually is the only means of arriving at a diagnosis before operation The technic of the roentgen examination is difficult and must be carried out with great accuracy and care The presence of a hernia may be detected occasionally with the patient in the erect position If the sac is filled with air, the gas bubble can be visualized above the diaphragm. The herniated portion of the stomach may contain both air and liquid, in which case the fluid level with gas above gives a clue to the diagnosis. Even on the ingestion of the opaque meal, fluoroscopic studies with the patient standing only rarely demonstrate the presence of a hernia. In only three cases of our series did the pouch fill while the patient was in the erect position, and in two of these the hernia reduced itself and disappeared during fluoroscopy. As a rule therefore, the examination in the standing position gives no intimation of the existence of this lesion. If the roentgen studies are carried out in this position only, as is done in some clinics, these hernias will be overlooked.

It is with the patient lying on the fluoroscopic table and the stomach well filled with the opaque mixture that the hernia is most apt to be visualized. There is no single position in which it is possible to bring the lesion into view in every instance. It is essential to observe the patient in the prone, supine and oblique positions. Deep inhalation and exhalation should be advised during the time of observation. Pressure on the abdomen with the gloved hand is important to force the gastric content into the cardia. Lowering the head of the table or placing a pillow under the buttocks is an important maneuver.

Roentgenograms of this lesion are difficult to obtain and even with the most careful technic frequently fail to show the hernia. This is due to the fact that the hernia is usually relatively small and is overlapped by the diaphragm, the cardiac shadow, the spine, and, in females, the breasts. Numerous films in different positions are necessary. In several instances, the hernia has been visualized fluoroscopically but could not be demonstrated on the roentgenograms. The most satisfactory procedure for overcoming this difficulty is to determine the best position for demonstrating the lesion with the fluoroscope, and then to replace the fluoroscopic screen with a film and make the exposure with the same tube that was used during fluoroscopy. Serial roentgenograms may be of great value.

After the ingestion of the barium meal, the herniated portion of the stomach is seen as a round or ovoid shadow lying just above the diaphragm in the region of the lower end of the esophagus. The hernia is usually near or in the median line and projects more to the right than does the lesser curvature. As a rule, there is a direct connection between the opaque medium in the upper portion of the cardia and the barium in the hernia, the two being united by an isthmus at the level of the esophageal hiatus. In some instances, the lesion lies entirely above the diaphragm and does not appear to connect directly with the stomach. The size and shape of the hernia may vary with the degree of filling, the patient's position, the phase of respiration, and the amount of intra-abdominal tension. When the herniated portion of the stomach is completely filled with barium, it is seen as a smooth, sharply defined shadow which is of uniform density throughout. If it is only partly filled with the opaque mixture and contains air also, the gas collects in the upper portion, giving a mottled shadow. With the patient standing, a fluid level with a horizontal upper border is seen. If the sac contains only a little barium the rugae of the stomach are visualized. This is a very important observation as it proves conclusively that the shadow lying above the diaphragm actually is a portion of the stomach. The lesion may reduce itself during the roentgen examination. This occurs most commonly when the patient turns or changes from a lying to a standing position. While reduction and consequent disappearance of the hernia increase the difficulties of diagnosis from the roentgenologic point of view, this phenomenon is very important clinically as it proves the absence of adhesions and that there is little or no danger of incarceration.

The relation of the esophagus to the hernia should be studied carefully in every instance. This is best accomplished by giving the patient a few additional swallows of the opaque mixture after the hernia has been visualized. Films may be made while the liquid is being swallowed or fluoroscopic studies may be carried out. Usually, the lower esophagus is seen to be normal. Rarely, it may be tortuous, the tortuosity disappearing when the hernia reduces itself. In two of our patients who complained of dysphagia, there was slight dilatation of the esophagus with delay at the lower end, apparently due to the fact that the hernia pressed on the esophagus and caused a partial obstruction. The hernia may be to the left, right, front or back of the esophagus, in some cases it may partially surround the esophagus. The stomach usually rises high, so that the cardia lies in close contact with the diaphragm. In several cases the stomach appeared to be more to the right than normally. The cardia may be smaller and much less rounded than usual.

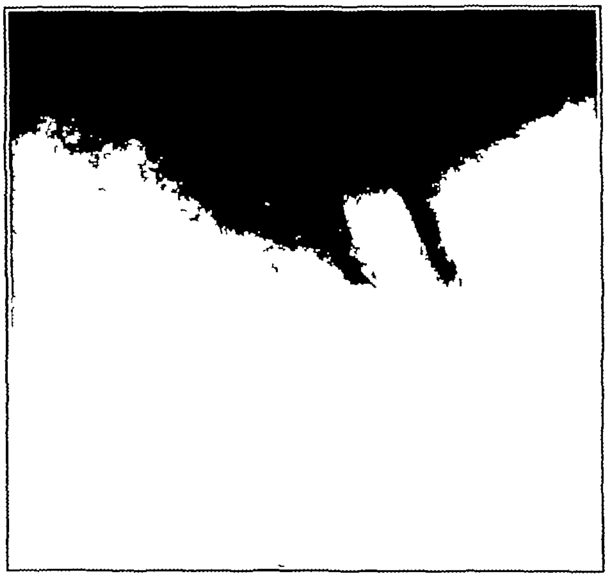


Fig 7.—Diverticulum of the stomach. The barium filled diverticulum lies just medial to the cardia and below the diaphragm. At the six hour observation the stomach was empty but the diverticulum remained filled with the opaque mixture.

DIFFERENTIAL DIAGNOSIS

From the clinical standpoint, the common conditions to be considered in differential diagnosis are carcinoma of the stomach, peptic ulcer, gallbladder disease, carcinoma of the lower end of the esophagus, and angina. Each of these conditions usually has its typical history and clinical evidence. It is in atypical or borderline cases that diagnosis becomes difficult and the possibility of esophageal orifice hernia should be considered. If this lesion is borne in mind both the clinician and the roentgenologist will diagnose it with greater frequency. As more cases of this type of hernia are recognized and recorded in the literature, the clinical picture will become more clearly defined and this condition will take its rightful place as a not uncommon cause of upper abdominal symptoms.

From the roentgen point of view, it is necessary to consider the following conditions in differential diagnosis diaphragmatic hernia of other types, diverticulum of the lower esophagus, diverticulum of the stomach, cardiospasm, cardio-esophageal relaxation, eventration Diaphragmatic hernias of other than the esophageal orifice type may be the result of a congenital abnormality, severe trauma to the abdomen, a gunshot injury or a stab wound These hernias may involve any part of the diaphragm In esophageal orifice hernia, only the stomach passes into the thorax Portions of the small intestine, the colon, the stomach and other abdominal organs may be involved in the other types of diaphragmatic hernia The relation of the esophagus to the lesion may be demonstrated roentgenologically by the use of the opaque meal, proving conclusively whether the lesion involves the esophageal orifice or some other portion of the diaphragm Diverticulum of the esophagus is attached to the esophagus and always lies in direct contact with it The shadow of a hernia through the esophageal orifice can be shown to be connected with the stomach and may be differentiated from the esophageal outline as the patient is studied in the various positions fluoroscopically A diverticulum fills directly from the esophagus while a hernia, as a rule fills from the stomach The former is usually well above the diaphragm and is best seen with the patient erect the latter lies in direct contact with the diaphragm and is seldom visualized except in the recumbent position

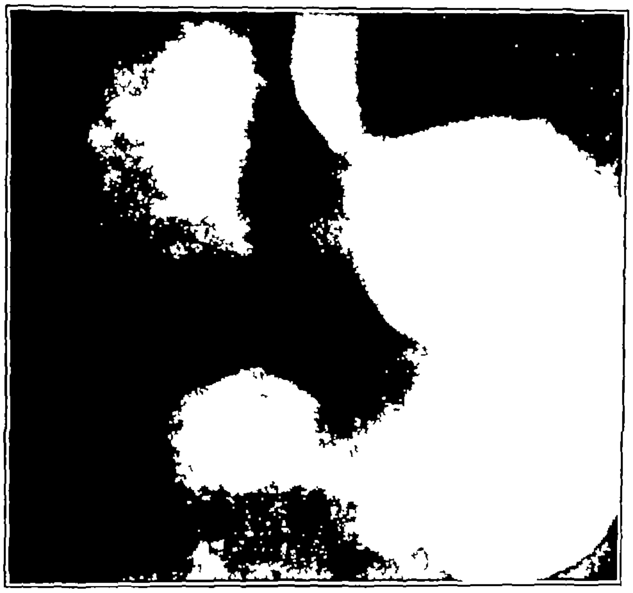


Fig 8—Cardio-esophageal relaxation The opaque meal flows back into the esophagus from the stomach This condition can be differentiated from esophageal orifice hernia by giving the patient a few swallows of barium and demonstrating that the shadow above the diaphragm is the esophagus and not a portion of the cardia of the stomach

Diverticulum of the stomach is a projection from the gastric lumen and is below the level of the diaphragm There is very frequently retention of some of the barium mixture in the diverticulum after the main mass of barium has passed out of the stomach while an esophageal orifice hernia empties itself during the emptying of the stomach A diverticulum is best visualized with the patient erect, while an esophageal orifice hernia is rarely seen in this position Cardiospasm is an obstruction of the lower end of the esophagus with dilatation of the esophagus of varying degree and should not cause confusion In cardio-esophageal relaxation, the opaque meal flows freely into the stomach and then runs back into the esophagus when the patient is recumbent There is no circumscribed shadow above the diaphragm as in esophageal orifice hernia, and fluoroscopic studies make the differential diagnosis easy Eventration is an elevation of the diaphragm with a resultant high position of the stomach, splenic flexure, and small bowel The differentiation between this condition and esophageal orifice hernia depends on the visualization of the diaphragm and the demonstration that in eventration the stomach lies below the elevated diaphragm This is usually possible after the administration of a barium sulphate meal If this method fails, the diaphragm may be visualized by administering a compound effervescing powder in order to distend the stomach with gas Fluoroscopic observations with the patient in the erect position after the stomach has been filled with gas or the opaque meal have always enabled me to demonstrate the position of the diaphragm and thus determine whether I was dealing with eventration or an orifice type of hernia

TREATMENT

The medical treatment of esophageal orifice hernia is symptomatic and consists mainly of dietetic and preventive measures Thorough mastication, slow eating and small meals are advisable Fluid in considerable amounts may be taken with the meals The patient should not lie down after having eaten If distress comes on during or soon after eating, walking about for a few moments or a hot drink usually gives relief The avoidance of straining, tight bands about the abdomen and other causes of increased intra-abdominal pressure is important If the symptoms are severe and unrelieved by medical treatment, surgery may be resorted to The operation is difficult and should be undertaken only after careful consideration of the patient s general condition The abdominal approach is preferable A large incision is necessary, adequate exposure being the first requisite The hernia is reduced completely and the esophageal opening of the diaphragm sutured to its normal size As the difficulties of operation are greatly increased by the respiratory movements of the diaphragm, phrenicotomy may be performed on the left side as a preliminary step In patients who cannot undergo the extensive abdominal operation necessary to cure an esophageal orifice hernia phrenicotomy may give symptomatic relief Fortunately, the complaints are mild in the great majority of cases and surgical intervention is rarely necessary Only three cases of our series came to operation

SUMMARY

An esophageal orifice hernia is a protrusion of a portion of the cardia of the stomach through the esophageal opening of the diaphragm into the thorax This type of diaphragmatic hernia was formerly considered very rare and therefore of but slight clinical significance With the increasing use of the roentgen ray in the examination of the gastro-intestinal tract, it is being found with increasing frequency and several large series of cases have been reported during the last decade

The present series consists of sixty cases, all diagnosed during the routine roentgen examination of the stomach with the opaque meal These occurred over a period of five years, during which time about 8,000 gastro-intestinal cases were studied roentgenologically

Enlargement of the esophageal orifice of the diaphragm with resultant herniation of the cardia may be congenital or acquired The acquired cases are due to increased intra-abdominal tension plus some unknown factor which accounts for the herniation being through the esophageal hiatus rather than at one of the commoner sites of hernia

My series comprised forty-one females and nineteen males The ages varied from 21 to 72 years, the majority of the patients being over 40

In fourteen patients there were no symptoms referable to the hernia The remainder had complaints of varying degrees of severity The commonest symptoms were epigastric pain, heartburn, nausea, vomiting, regurgitation and constipation As a rule, the symptoms are rather indefinite, mild in degree, and of years' duration The most typical complaint was a feeling of weight or pressure under the xiphoid, coming on during or soon after eating and relieved by a hot drink or by walking about for a few moments

Small hernias give no physical signs Large hernias may simulate pneumothorax or hydrothorax

The roentgen examination is usually the only means of arriving at a diagnosis Very careful studies are essential to demonstrate this lesion Fluoroscopic observations in the prone, supine and oblique positions must be made, as the hernia is only rarely seen with the patient erect and is difficult of roentgen demonstration

After the ingestion of the opaque meal, the hernia is seen as a round or ovoid shadow just above the diaphragm, it lies in or near the median line, usually to the left of the esophagus The hernia as a rule connects with the stomach by an isthmus at the level of the esophageal orifice

Roentgenologically, this condition must be differentiated from diaphragmatic hernia of other types, diverticulum of the esophagus and stomach, cardiospasm, cardio-esophageal relaxation and eventration

Treatment consists mainly of dietetic and preventive measures Surgical operation is indicated if the symptoms are severe As a rule, however, the complaints are mild and operative measures are only rarely necessary

485 Commonwealth Avenue

ABSTRACT OF DISCUSSION

Dr. A L Gray, Richmond, Va This paper is a monograph on esophageal orifice hernia that should be in the laboratory of every roentgenologist It is the most complete discussion of the subject that I have ever heard There are several points on which I should like to lay a little additional stress Many of the small laboratories throughout the country have only a vertical fluoroscope, and it is absolutely impossible, as the author stated, to show a reducible hernia of the esophageal orifice with an upright fluoroscope If it is incarcerated we may be able as he said, to see an air bubble or gas bubble above the diaphragm. That, however, would not be differentiated from a lower end esophageal diverticulum However, in incarcerated conditions I have occasionally been able to suspect and therefore search more diligently for the real condition by reason of a longitudinal shortening at the expense of the upper pole of the stomach Of course, the shortening alone would not differentiate between an esophageal hernia and an extensive carcinomatous lesion of the cardiac end of the stomach The only real method of determining the presence of esophageal hernia is by the dorsal position and preferably with the hips well elevated above the level of the shoulder or sometimes it may require an almost complete inversion such as is possible by means of our modern tables The lateral position, the patient being rotated toward the left side will often give us valuable information It is my routine after making an upright fluoroscopic examination to place the patient in the dorsal position with pressure on the lower pole of the stomach and then to rotate the patient toward the left side If the upper pole of the stomach is smooth and there is no tendency to herniation, I then rotate the patient gradually toward the right side, making careful observations all the time.

Dr. Cassie Belle Rose, Chicago In the Presbyterian Hospital of Chicago, we search for these esophageal herniations in all examinations of the stomach and find them often enough to make this routine worth while In my experience the differentiation from carcinoma of the lower end of the esophagus is the important point If, in the patients with symptoms the patient gets the idea that he has a cancer and one can definitely say that he has not—that he has only an esophageal herniation—the mental relief of the patient is worth a great deal Then in fact, the differential diagnosis becomes the chief treatment.

Dr. Max Ritvo Boston In the past there has been no agreement among authors as to a name for these hernias In the literature, we find papers on this subject entitled, Herniation of a Portion of the Fundus of the Stomach Through the Esophageal Hiatus of the Diaphragm," 'Diaphragmatic Hernia of the Stomach Through the Esophageal Opening" and so on These names are descriptive, but very long and too cumbersome for ordinary use If we as roentgenologists can agree on a short, simple title, it will help the study of this condition greatly The name "esophageal orifice hernia' has the great advantage of conciseness, as well as describing what the condition is and where it is The traumatic type of diaphragmatic hernia has not been included as it does not come into the group under discussion As the result of severe trauma to the abdomen the diaphragm may be ruptured. The stomach intestines, spleen and various other abdominal organs may herniate through this opening into the thoracic cavity In the esophageal orifice type of hernia, however, only the stomach is involved and even with very large hernias we have never seen any organ other than *the stomach herniate into the thorax*

ACCIDENTAL PNEUMOTHORAX *

JOSEPH L HARVEY M D

DENVER

My object in this paper is to contrast two cases of pneumothorax which followed fractured ribs Only one case similar to case 2 was found in the literature [1] The term pneumothorax was probably first used in 1803 by Itard to denote air or gas in the pleural cavity Hippocrates noted the succussion splash, and Laënnec in 1819 gave such a thorough description of the symptoms and signs that little has been added since

Pneumothorax is regarded by some as of very minor importance, by others as an extremely serious condition Most interns believe that pneumothorax is such a simple matter that they are fully qualified to perform artificial pneumothorax In Denver, even simultaneous bilateral artificial pneumothorax is being done now in selected cases The first paragraph of the chapter on pneumothorax in Fishberg s book on Pulmonary Tuberculosis emphasizes the other view

> This is the most frightful complication of pulmonary tuberculosis It is of more significance than copious pulmonary hemorrhage because the latter only terrifies the patient, and the ultimate prognosis is usually favorable but pneumothorax is deadly and the victim is justified in his apprehension that the collapse and agonizing dyspnea are indications that he is breathing his last. From West s statistics it appears that 70 *per cent of patients* attacked by *pneumothorax* die, and in phthisis the proportion is even higher

These statistics [2] are also quoted in the 1927 edition of Osler s Practice of Medicine The difference between these extreme views can be partially accounted for by the fact that one refers to spontaneous pneumothorax with a rupture of the visceral pleura, while the other refers to a carefully controlled artificial pneumothorax. Recent data on pneumothorax give a mortality of from 10 to more than 80 per cent depending on the type of pneumothorax, and the time interval allowed before death occurs

---

* From the Department of Roentgenology University of Colorado School of Medicine and Hospitals

* Read before the Section on *Radiology* at the Eightieth Annual Session of the American Medical Association Portland Ore July 12 1929

[1] Sante L R Massive Collapse of the Lung Am J Roentgenol **20** 213 (Sept) 1928

[2] Lancet 1897

REPORT OF CASES

Case 1—Mrs L S, aged 27, was injured in an automobile accident in December, 1928 Her chief complaint was pain in the right side of the chest, localized over the lower ribs There was no expectoration of blood At the age of 15 she had been kicked by a horse and three ribs on the right side were broken, otherwise she had never been sick or injured

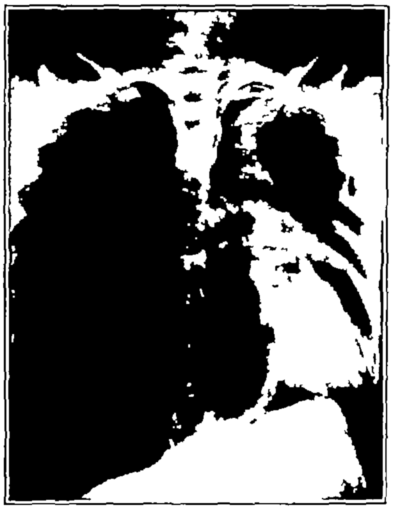


Fig 1—Enormous pneumothorax following fracture of tenth right rib

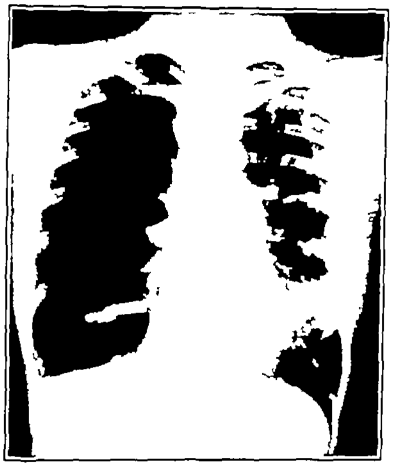


Fig 2—Degree of pneumothorax which is persistent after six months

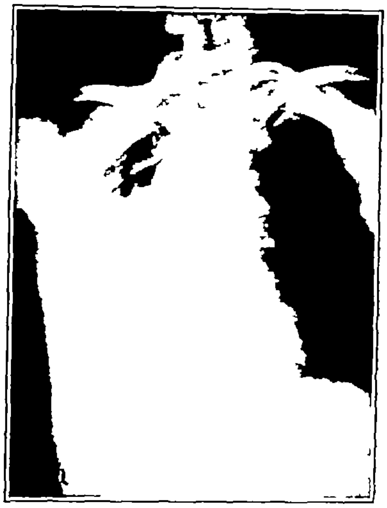


Fig 3—Pneumothorax in upper right side of chest lower right side dull heart and mediastinum shifted markedly to the right.

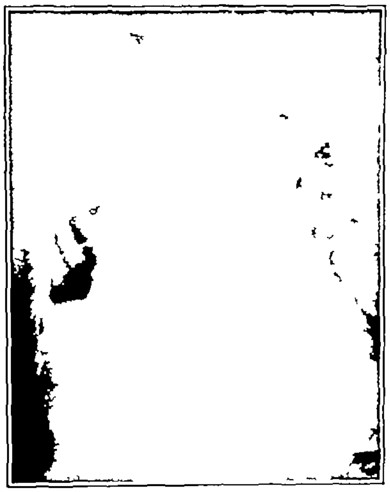


Fig 4—Oblique view showing pneumothorax area more definitely and fluid (blood) level

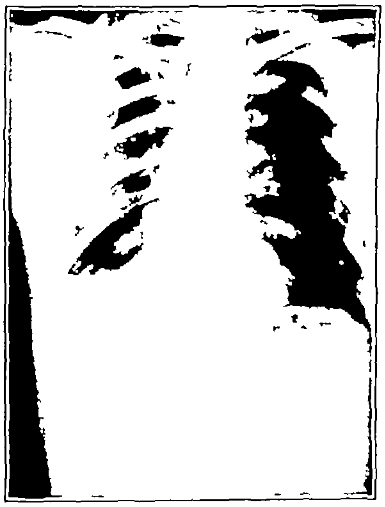


Fig 5—Forty-eight hours after accident and a few hours after the coughing up of several blood clots. Definite return of heart and mediastinum toward normal position.

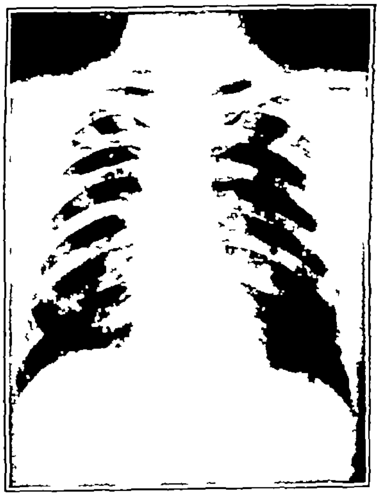


Fig 6—Three months after accident. There are slight evidences of old tuberculosis thickened pleura is present over the site of the fractured rib

On examination the patient was very pale and in shock. Other observations were irrelevant, except for the chest There was crepitation of subcutaneous air over the lower ribs and in the right axilla, and extreme hyperresonance over the entire right side of the chest

The apex beat was strong in the fifth interspace in the left axilla

Roentgen examination showed a recent fracture of the tenth rib with some displacement, the mediastinum was displaced 7 cm to the left, the heart was displaced tightly against the left axillary chest wall, and the right half of the diaphragm was concave, depressed down to the twelfth rib

A diagnosis of enormous pneumothorax and fractured rib was made (fig 1)

For the first four days 1,000 cc of air was aspirated daily, with constant improvement After the removal of the first thousand cubic centimeters of air there was a drop in the pulse rate from 120 to 86 per minute. On the second day the left border of the heart was 1 5 cm from the chest wall, on the seventh day there was 4 cm clearance A small amount of fluid formed which was gradually absorbed On the sixteenth day roentgen examinations, before and after the aspiration of a large amount of air, showed an increase in the amount of air after the aspiration, proving a valvular pneumothorax. There has been little, if any, change in the pneumothorax for six months (fig 2)

Case 2—G D E, a man aged 38, who had come to Colorado sixteen years before on account of tuberculosis of the right apex, was admitted to the hospital following an automobile accident, Feb 16, 1929 Examination showed lacerations and abrasions of the face and back, also a bruise of the left foot On coughing or deep respiration he had pain just lateral to the right nipple, and restriction of motion on the right side. There was some hemoptysis for two hours following the accident. The total

Vincent s infection of the larynx in a child, aged 2½ years, extend into the lungs, producing abscess, empyema and death Typical Vincent's organisms were cultivated from the lungs and pleural fluid at necropsy Lewis and Barenberg[4] reported a similar case in a 3 year old child in whom a Vincent's infection of the larynx extended into the lungs, producing fatal pulmonary gangrene Chevalier Jackson[5] studied with the aid of the bronchoscope a case in which the Vincent's infection of the pharynx was followed by ulceration of the bronchi He made smears through the bronchoscope from the deep ulcers in the bronchi and found that the fusiform bacilli and spirochetes were present in practically pure culture Two of my cases belong to this group in which there was direct extension of the infection from the upper respiratory tract to the lungs

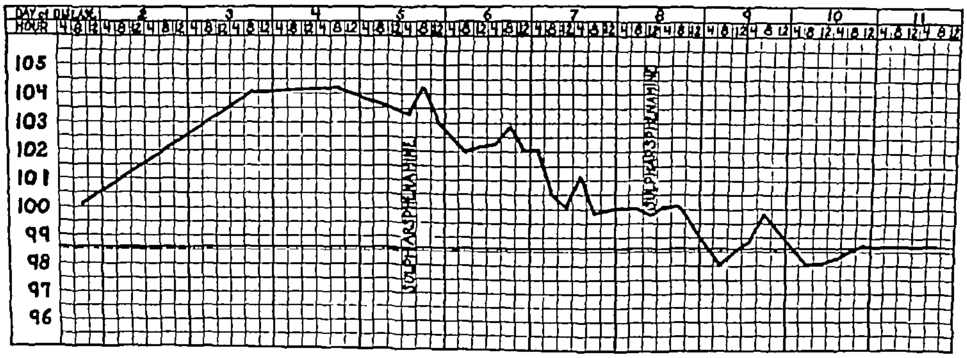


Fig 1 —Temperature curve in case 3 showing the dates when sulpharsphenamine was administered

In a second clinical type of this infection the primary lesion is found in the bronchi or lungs Rothwell[6] in 1910 recorded two cases in which Vincent's organisms were present in large numbers in the bloody sputum He named the disease "bronchial Vincent's angina" Campbell and Dyas[7] observed cases of primary acute bronchitis during an epidemic of Vincent's angina among Canadian troops stationed in England They found large numbers of fusiform bacilli and spirochetes in the sputum from these patients Peters,[8] Gifford,[9] McNeill,[10] Marshall,[11] Wahl,[12] Cahan,[13] Greeley,[14] Kline and Berger,[15] Pilot and Davis,[16] Rohdenburg[17] and I[18] have reported cases of primary infection of the lung and bronchi with these organisms In my third case there were no signs of infection in the throat, the pulmonary lesion appearing four days after exposure to a patient with Vincent's angina

REPORT OF CASES

Case 1 —O B, a white man, aged 30, a laborer, had always been in good health before the present illness Oct. 20, 1927, his wife developed tonsillitis, which was subsequently proved to be a Vincent s infection About ten days later, November 1, the patient himself noticed general weakness and some soreness of the throat. The symptoms were more marked, November 2, so he remained in bed

I saw him, November 3, when the temperature was 103 F and the pulse 90 There was a slight fetid odor to the breath, and examination of the throat revealed a large necrotic ulcer on the right tonsil. Smears from the diseased area showed large numbers of typical Vincent's organisms The lesion was treated by local applications of solution of potassium arsenite (Fowler's solution) The next day the throat was less painful, but during the night a cough had developed which was productive of about 20 cc of thick greenish sputum without odor Examination of the chest revealed a small area of rales just below the angle of the left scapula There were no definite changes in percussion or in the breath sounds over this area The sputum contained large numbers of fusiform bacilli and spirochetes indistinguishable morphologically from those in the tonsil of the patient and from the throat of his wife A guinea-pig inoculated in the groin with 1 cc of sputum developed a large fusospirochetal abscess

November 5 the patient was much better, although the productive cough persisted On the same day and on November 15, the patient was given 0 6 Gm of sulpharsphenamine intravenously A reexamination six months later failed to show any evidence of pulmonary disease by physical signs or a chest roentgenogram

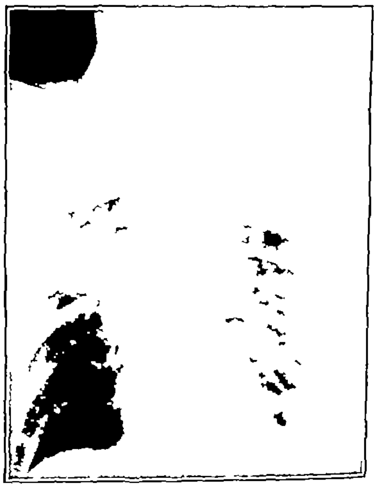


Fig 2 —Chest roentgenogram in case 3 (portable apparatus) made at the height of the disease. The area of involvement in the right lung has been surrounded with a dotted line.

Case 2 —H D H, a white man, aged 27, a physician, attended a patient with an acute Vincent's infection of the tonsils from May 22 to June 10 He assisted in the transfer of some of the membrane from the throat of the patient to the groin of two guinea-pigs and later performed an autopsy on the pigs June 8, he noticed a slight pharyngitis which gradually increased in severity until June 14, when the tonsils became markedly swollen and inflamed and enlarged glands appeared in the neck On that evening the patient became nauseated and vomited There were general malaise and profuse perspiration on exertion, but he returned to work the next day as usual

---

[4] Lewis J M and Barenberg L H Pulmonary Gangrene Due to Spirochetes and Fusiform Bacilli Am. J Dis Child **37** 35 (Feb) 1929

[5] Jackson Chevalier Ulcerative Bronchitis Due to Vincent s Organisms J A M A **83**: 1845 (Dec. 6) 1924

[6] Rothwell J H Bronchial Vincent s Angina J A. M A. **54** 1867 (June 4) 1910

[7] Campbell A R. and Dyas A. D Epidemic Ulceromembranous Stomatitis (Vincent s Angina) Affecting Troops J A M A. **68** 1596 (June 2) 1917

[8] Peters W H *Hand Infection Apparently Due to Bacillus Fusiformis* J Infect. Dis **8** 455 (June) 1911

[9] Gifford S R Fusiform Bacilli of Vincent s Angina J Bact. **5** 365 (July) 1920

[10] McNeill Pulmonary Infection with Spirochetes and Fusiform Bacilli of Vincent s, Bull Johns Hopkins Hosp **35** 368 (Nov) 1924

[11] Marshall Infection of the Lungs with Vincent s Spirillum Kentucky M J **23** 3800 (July) 1925

[12] Wahl H R The Pathology of Some Unusual Pulmonary Lesions South M J **19**: 591 (Aug) 1926

[13] Cahan J M Pneumonitis Caused by Vincent s Organism M J & Rec. **125** 194 (Feb 2) 1927

[14] Greeley Horace Vincent s Angina Infection Its Prevalence Varied Manifestations Treatment and Bacteriology Am J M Sc **155**: 742 (May) 1918

[15] Kline B S and Berger S S Spirochetal Pulmonary Gangrene Treated with Arsphenamine J A. M A **85** 1452 (Nov 7) 1925

[16] Pilot Isadore and Davis D J Fusiform Bacilli and Spirochetes Their Role in Pulmonary Abscess Gangrene and Bronchiectasis Arch Int Med **34** 313 (Sept) 1924

[17] Rohdenburg Pathological Conditions Associated with the Presence of Fusiform Bacilli and Spirilla Proc New York Path Soc N S **24** 177 1924

[18] Smith D T Bronchopulmonary Spirochetosis Am Rev Tuberc **15** 352 (March) 1927

The tonsils presented the picture of a severe follicular tonsillitis, and smears from them showed cocci, vibrios, fusiform bacilli and spirilla. June 15, the throat was about the same but the cervical glands were more enlarged On this day, subcutaneous injections of sodium cacodylate were started By the next day the glands were less tender and slightly smaller Dark field examination of the fluid from the tonsils showed spirochetes, fusiform bacilli, cocci and vibrios Daily injections of sodium cacodylate were continued and the throat was swabbed twice daily with solution of potassium arsenite until June 20, when symptoms of mild stomatitis appeared and all medication was discontinued The throat healed the glands steadily decreased in size, but the malaise and the temperature of from 99 to 99 4 persisted

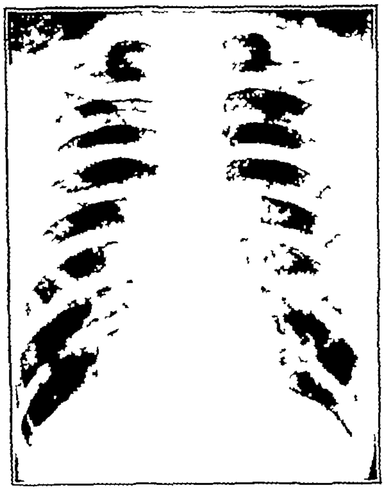


Fig 3—Roentgenogram of the chest in case 3 ten days later

June 29 the temperature reached 101 in the evening and that night the patient had severe profuse sweats The throat was not sore but there was a nonproductive cough and his family observed an extremely foul odor to the breath He was admitted to the hospital, June 30 Physical examination revealed slight dulness near the left base in front, and rales were heard over this area when the patient coughed The chest roentgenogram showed soft mottled shadows in this region The day following his admission to the hospital he began to raise a small amount of green sputum which had a slightly foul odor Examination of the sputum showed no tubercle bacilli, but spirochetes fusiform bacilli, cocci and vibrios were present. The fresh untreated sputum in 1 cc. amounts produced a typical fusospirochetal abscess when injected into the groin of guinea-pigs The guinea-pig that was inoculated with the concentrated sputum failed to develop tuberculosis

For the first few days in the hospital the temperature varied from 98 6 in the morning to 102 and 103 in the afternoon July 4, 0 45 Gm of sulpharsphenamine was given intravenously, followed by 0 6 Gm, July 8 The day after the first treatment the cough was looser, and both cough and expectoration diminished rapidly and disappeared completely in a few days A week later the temperature was normal, the physical signs had disappeared, and the chest roentgenogram showed the left base clear After another week in bed the patient left the hospital apparently convalescent. Shortly afterward, he began to register a temperature of from 99 6 to 100 6 and was readmitted, August 4 The physical examination and chest roentgenogram showed no evidence of the previous infection, but because of the persistent elevation of temperature, two more injections of sulpharsphenamine were given, August 15 and 20 He continued to have a temperature of from 99 to 99 8 two or three evenings in the week until November 15 A gain of 30 pounds (13 6 kg) was made during this period and he returned to work Jan 1, 1929

Physical examination and a chest roentgenogram made six months later revealed no evidence of the disease It is significant that in this patient, as in the one treated by Chevalier Jackson, the first pulmonary symptoms developed some time after the lesion in the pharynx had disappeared.

Case 3—W W., a man aged 29, a physician four days after examining and treating the throat of a patient with severe Vincent s infection returned home in the evening of Aug 29 1927 complaining of headache and backache The symptoms grew worse during the next day and a slight cough developed accompanied by a small amount of mucoid sputum. That evening, August 30 the temperature was 102 F August 31, he was very restless the temperature reached 104 in the evening and was followed by a rigor and profuse perspiration. September 1, the sputum became purulent, he was slightly irrational, and the temperature reached 104.2, followed by rigor and perspiration The following day, the patient was examined by a colleague who found slight suppression of the breath sounds at the base of the right lung posteriorly but no other evidence of pulmonary disease Specimens taken by me on the same day for blood, stool and urine culture were negative for typhoid bacilli, and the Widal reaction was negative The blood count showed 12,000 white cells with a differential count of 83 per cent polymorphonuclears 13 per cent lymphocytes and 4 per cent monocytes The urine examination showed a trace of albumin, a moderate number of white blood cells and a few red cells but no casts The sputum was thick, green and purulent, and about 30 cc. was expectorated No tubercle bacilli were found but enormous numbers of fusiform bacilli, spirochetes, vibrios and cocci were present (fig 4 *B*)

The next day slight dulness suppression of the breath sounds and a few rales were heard at the base of the right lung posteriorly and a chest roentgenogram revealed circumscribed shadows projecting out from the hilum into the right lung (fig 2) In view of the presence of fusiform bacilli and spirochetes in the sputum the patient was given 0 6 Gm of sulpharsphenamine intramuscularly on the afternoon of September 2, which was the fifth day of the disease September 3, he was somewhat better, the temperature was 103 6, the pulse 100, and the respiration 20 The sputum remained unchanged in amount and in physical characteristics, but the microscopic examination showed only a few fusiform bacilli and no spirochetes September 4, the temperature was 101 6 and numerous moist rales were heard over the area of dulness The sputum was somewhat reduced in amount and thinner in consistency, and repeated examination failed to show either the large fusiform bacilli or the spirochetes although all the other organisms were still present (fig 4 *C*)

September 5, the patient was given 0 6 Gm of sulpharsphenamine intravenously, following which the sputum rapidly decreased, the temperature returned to normal (fig 1), and the physical signs in the chest disappeared A chest roentgenogram made September 10 showed that the shadows had disappeared (fig 3) After a few weeks' rest he returned to his practice and is still well and free from symptoms more than two years after his illness

BACTERIOLOGY OF THE SPUTUM

The sputum in case 3 was thick, green, purulent and without odor It was similar in appearance to tuberculous sputum, although at no time were tubercle bacilli demonstrated either by smear or by guinea-pig inoculation The sputum was studied with various stains, the dark field apparatus and with aerobic and anaerobic cultures Both the large and the small types of the fusiform bacilli[19] were isolated The spirochetes were

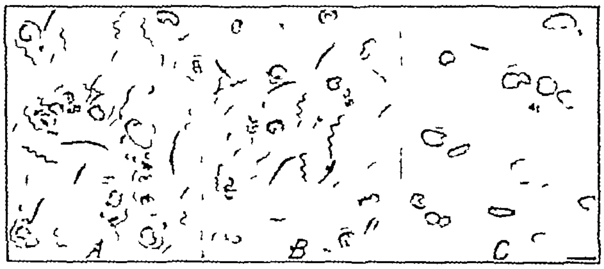


Fig 4—Camera lucida drawings of smears stained with gentian violet *A* smear from pharynx in case of Vincent s angina which was being treated by Dr W W *B* smear from Dr W W s sputum before treatment *C* smear from Dr W W s sputum twenty four hours after the first injection of sulpharsphenamine

predominantly of the *Spirochaeta vincenti* type, with smaller numbers of *Treponema microdentium*, both were cultivated but only the latter were isolated in pure culture The vibrio was not isolated but seemed to be identical with that usually found in Vincent's angina Also *Staphylococcus albus*, hemolytic and nonhemolytic streptococci and an unidentified gram-negative gas-forming organism were isolated

---

[19] Smith D T Fusospirochetal Disease of the Lungs Its Bacteriology Pathology and Experimental Reproductions Am. Rev Tuberc. 16 584 (Nov) 1927

Two guinea-pigs were inoculated in the groin with 1 cc each of sputum which was obtained on the fifth day of the disease and before the sulpharsphenamine was given One pig died four days later with an abscess in the groin and multiple metastatic abscesses of the liver, lungs and spleen The same combination of organisms was present in the metastatic abscesses as in the original sputum The second guinea-pig was killed after ten days and a large well walled-off abscess found in the groin which contained the same organisms as the original sputum except the gram-negative gas-former, which is frequently eliminated by passages through a guinea-pig[20] By inoculation of other animals in the groin, the disease was transmitted from pig to pig at ten day intervals for five passages

Pus from one of these pigs was inoculated in 0 25 cc amounts into the trachea of four rabbits Two rabbits died of pulmonary gangrene and two of pulmonary abscess associated with empyema

Sputum collected twenty-four and forty-eight hours after the patient had received his first injection of sulpharsphenamine had the same physical characteristics as the original, and contained the same organisms with the exception of the large fusiform bacilli and the spirochetes (fig 4 *C*) Injection of this sputum into the groin of guinea-pigs resulted in a local swelling which resolved without producing an abscess

Fortunately, at the time the physician (case 3) contracted the infection, a study of the bacteriology of Vincent's infection was being made at this hospital, and a complete record of the organisms present in the pharynx of his patient was available It was found that the germs present in the physician's sputum were in all respects identical with those in the pharynx of his patient (fig 4)

COMMENT

Vincent's angina, or fusospirochetal infection of the throat, is a relatively common and widespread disease and pulmonary complications due to these fusospirochetal organisms are by no means infrequent

The complicating pulmonary lesions often confused with pulmonary tuberculosis may take the form of pulmonary gangrene, pulmonary abscess, ulceration of the bronchi, lobar pneumonia, bronchopneumonia, and empyema

Many of these patients with pulmonary lesions recover spontaneously, but in some the condition terminates fatally It seems advisable to treat all cases in which fusospirochetal organisms can be demonstrated in the pulmonary sputum with either neoarsphenamine or sulpharsphenamine To obtain the best results the diagnosis should be made and the arsenic given before there is any appreciable destruction of pulmonary tissue The cases recorded here were treated on the third, fourth and fifth days, respectively, of the illness

CONCLUSIONS

1 The three cases of fusospirochetal disease of the lungs reported here followed contact with cases of Vincent's angina

2 Two cases were primary infections of the pharynx with subsequent extension into the lungs

3 The third case was primary in the lungs and began four days after contact with a case of Vincent's angina

4 In all three cases recovery was prompt after the administration of sulpharsphenamine

---

Clinical Notes, Suggestions and New Instruments

VEIN RETAINER

R. E. Tyvand, M D Chicago

Every one at times has difficulty in entering the lumen of a vein for intravenous therapy To aid in making a vein more accessible for this purpose and thereby simplifying intravenous work, the instrument presented here has been devised To my knowledge, no similar device has been described in the literature or used by the medical profession.

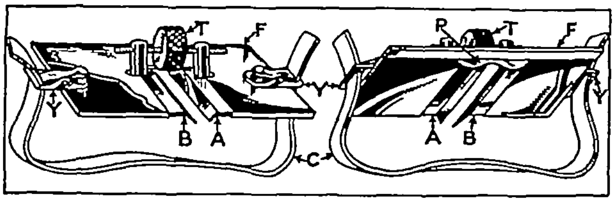


Fig 1 —Diagrammatic representation of vein retainer

The instrument consists of a metal frame piece, *F*, on the undersurface of which are fitted two shutter plates, *A* and *B* with downward bent edges which can simultaneously be made to approach or diverge from each other by the turning of the thumb screw, *T* The device is incorporated in a tourniquet cuff, *C*, as shown in figure 1, with self-retaining fasteners, *Y*, on each end of the frame piece

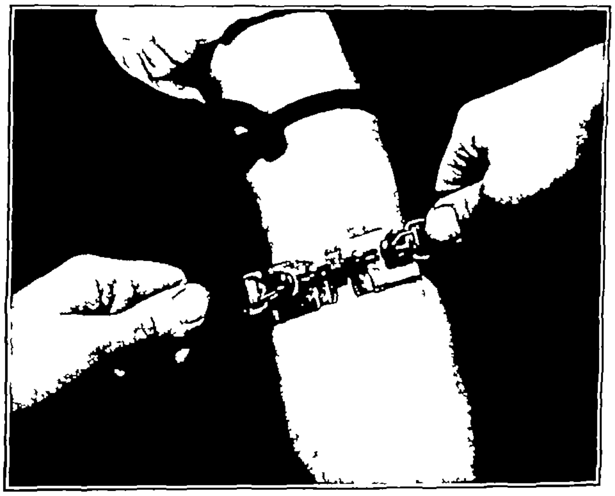


Fig 2 —Vein retainer in place on limb

In applying the instrument a constriction may be placed about the extremity above the desired site of application, causing the veins to fill and stand out as much as possible. Then, with the shutter plates well apart, the device is placed over the vein in such a manner that the open rectangular area falls over the vein and parallel to it. At the same time the notched perpendicular piece *P*, attached to the underneath surface of the frame piece, falls across the vein With gradual tension on the two ends of the cuff arrangement, pressure is brought to bear on the frame piece and by virtue of the notched perpendicular piece the vein tends to center in the aperture and

---

20 Smith D T Fusospirochetal Diseases of the Lungs Tubercle 9 420 (June) 1928

remains in place as a result of the embedding of the downward bent edges of the shutter plates With constant pressure on the frame piece the thumb screw is turned closing the aperture from each side of the vein while it is held in place and at the same time releasing skin tension over the vein and permitting it to fill more completely Thus, with the vein completely filled and held firmly in place, it is an easy procedure to insert a needle.

With the recent and rapidly developing demands for intravenous therapy along with the injection treatment of varicose veins I feel certain that this instrument will prove to be of benefit.

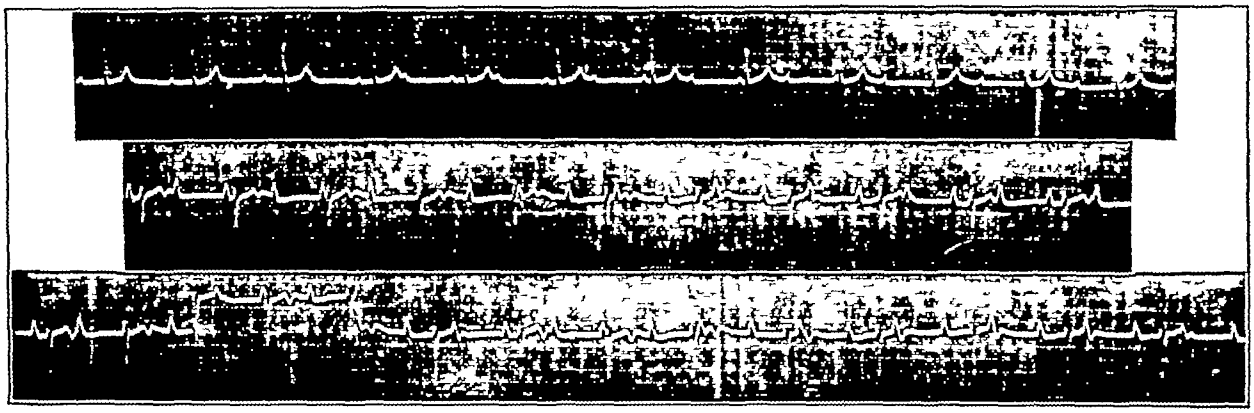
2449 Washington Boulevard

ASYMPTOMATIC HEART BLOCK OF LONG DURATION

Harold Thomas Hyman M D New York

The accompanying electrocardiogram shows a complete dissociation between auricle and ventricle. Each auricular beat occurs at an interval of 0 72 second (82 a minute) and each ventricular beat at 1 4 seconds (42 a minute)

The tracing in itself is not unusual, but the history of the patient from whom it was made is remarkable for its negativity The man is now 57 years old and has had an equally slow heart rate since he was 12 years old, if not before. He remembers distinctly that he was always able to obtain sick leave from school by having his pulse rate counted. At the age of 2 and again at 10 he had some protracted fever, both of which attacks were called typhoid and the details of which are no longer obtainable but they did not resemble diphtheria Since his school days he has worked in all corners of the world under arduous physical and mental conditions and now occupies an executive position of enormous importance Throughout all these years he has worked hard and played hard He has smoked cigarets constantly, he drinks moderately, he cannot remember ever having had a sick day, and the tracing that is shown here was made simply as a part of a routine physical examination.



Dissociation between auricle and ventricle in a case of asymptomatic heart block of long duration.

He has been a patient of mine for fourteen years during which time I was always aware of his slow pulse but unfortunately never before made any electrocardiographic tracings because he had no symptoms or signs of cardiac disease and was quite aware of the fact that his pulse rate had always been slow

There seems little doubt, therefore that this heart block dates back at least forty-five years, if not longer and probably originated in one of the infections of the patient s childhood. At the present time his physical condition is completely normal for a man of his age. The Wassermann reaction is negative The aortic arch is somewhat dilated The great vessels measure 5 4 cm. in the orthodiagram.

An extremely careful search of the literature and of the standard textbooks on cardiology fails to reveal any similar instance of a heart block of such long duration and rarely of one that is asymptomatic.

940 Park Avenue.

TRAUMATIC SEPARATION OF THE SYMPHYSIS PUBIS

Thomas D Sparrow M D Charlotte, N C

The literature is fairly prolific in reports of cases of separation of the symphysis pubis the result of parturition or some operative procedure incident to childbirth There are records available of exceptionally few cases in which the separation of the symphysis has occurred from other types of trauma. Of these the majority have been due to falls

G Schaanning[1] reports a case in a pregnant woman, almost at term who slipped and fell on the street. Willan[2] reports two cases and Buckley[3] one case resulting from falls from horses Koven s[4] case was due to an automobile accident.

I have been unable to find a case similar to the one reported in this article, in which a weight applied to the anterior superior spines of the ilium resulted in a sacro-iliac dislocation and the folding out of the pelvic ring

J B A., a man, aged 66, was admitted to the Charlotte Sanatorium because of pain across the lower portion of the abdomen. He stated that it had been necessary to jack up the rear wheels of his Ford truck in order to start the motor This done, he did not notice that the car was in reverse gear He lay down behind the car in order to lower the jack. As soon as the moving wheels struck the ground the car began backing and the rear wheel passed to the lower portion of the abdomen. The motor stalled' with the wheel of the loaded truck resting on the anterior superior spines of the ilium. He remained in this position for several minutes until a sufficient number of men gathered to lift the truck. He felt a severe pain in the lower portion of the abdomen and when lifted to his feet he was unable to stand. He was carried immediately to the hospital

The physical examination did not reveal anything abnormal in the head, neck or chest. There was marked extravasation of blood over the right iliac fossa extending about 1 inch below Poupart s ligament and over the entire scrotum. The symphysis pubis could be felt to be widely separated (fig 1) The patient was able to move both legs but the effort caused him severe pain. There was marked external rotation of both thighs and adduction and internal rotation was impossible. A catheterized specimen of urine showed only a few cubic centimeters of urine in the bladder Microscopic blood was present.

The patient was put to bed with a tight binder about the lower portion of the abdomen. Two days later he was suspended in the manner shown in figure 2. This suspension outfit consisted of two uprights with one longitudinally placed crossbar The pelvis was placed in a hammock consisting of canvas, double thickness, about 1¼ yards long The width of the canvas was sufficient to extend from the crest of the ilium to about 4 inches distal to the great trochanters of the femur This was lined with a liberal padding of cotton The free ends of the canvas were suspended from the crossbar, the ropes running through a series of pullies, and traction was maintained by weights To tighten the pelvic girdle, rope was laced from one side of the hammock to the other

---

[1] Schaanning G Rupture of the Pubic Symphysis Norsk Mag f Lægevidensk. 85 726-732 (Sept.) 1924 abstr J A M A 83 1468 (Nov 1) 1924

[2] Willan R. J Traumatic Symphysiotomy Surg Gynec. Obst. 45 389 390 (Sept.) 1927

[3] Buckley E. W Report of a Case of Separation of the Symphysis Pubis Fracture of the Ramus of the Pubis and Rupture of the Bladder M J Australia 1 422 (May 24) 1919

[4] Koven M T Traumatic Separation of the Sacro-Iliac Joint and Symphysis Pubis Am. J Surg 2 266 (March) 1927

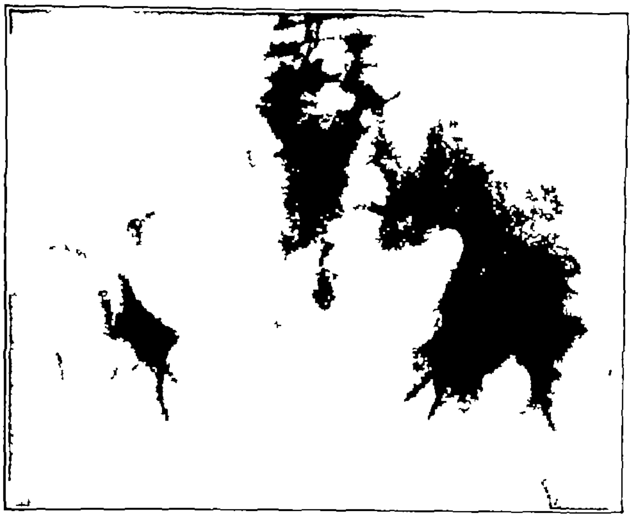


Fig 1 —Separation of symphysis pubis when patient was examined after admission to the hospital

This method successfully overcame the separation at the sacro-iliacs and at the symphysis Because of the development of a phlebitis in the right leg, and a perineal abscess, which was drained by Dr Squires of the Crowell Clinic, this method had to be abandoned During this treatment the pelvis was kept in a tight binder, but the separation recurred As soon as the drainage from the abscess cleared up sufficiently, the patient was strapped in an especially made low fitting belt This belt was applied six weeks after the accident, and sufficient union at the sacro-iliacs had occurred to prevent closure at the symphysis

He is, at the present time, walking about on crutches and refuses any attempt at improving his condition through operative intervention There was, at the beginning, a separation at the symphysis of 9 cm At present the separation is 6 cm in width Considerable improvement at the sacro-iliac joint is noticeable Brehm[5] states that any separation over 0 9 cm causes symptoms Beach[6] reports that a woman was injured during labor with 7.5 cm. separation After treatment there remained a separation of 3 cm, but the patient did not have any symptoms

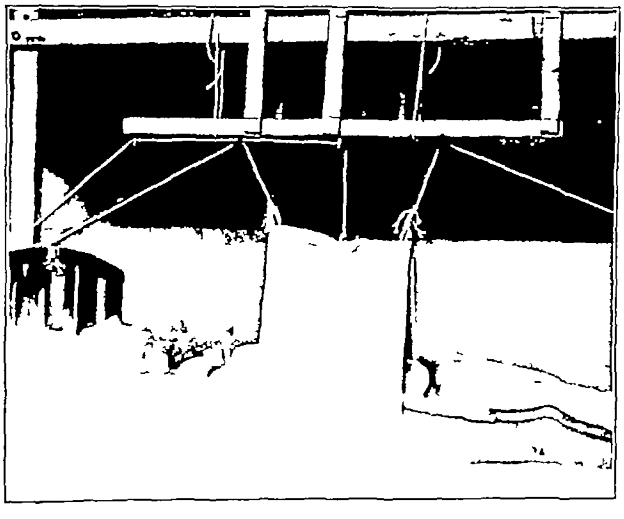


Fig 2 —Hammock method of treating separation of symphysis pubis.

Many methods have been suggested for treating separation of the symphysis Boorstein[7] reports six cases in which adhesive plaster and belts were employed with excellent results Allen[8] inserted a Lane plate. This did not hold and it had to be removed later Through two small skin incisions he then inserted two nails into the iliac spines, allowing them to protrude above the skin Strong wire was bound around these nails A cast was applied and after eight weeks the patient was able to walk. McNamara[9] closed the symphysis by passing number 4 silver wire through the obturator foramens This gave good results

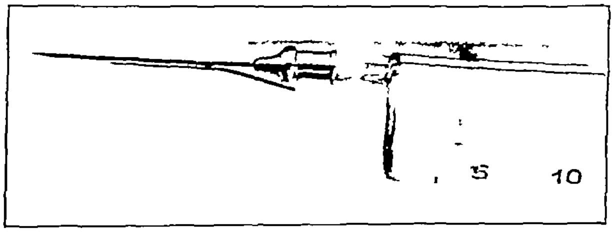
This case is reported (1) because of the unusual type of accident causing the separation (2) to record a separation of the pubis of such an extent in which there was no rupture of the bladder or fracture of the pelvis, and (3) to suggest this type of canvas hammock as a method of treatment in such cases

Professional Building

A NEW AMPULE NEEDLE *

George A. Clark, M D Scranton Pa.

During the last ten years, the use of serum has increased tremendously in the treatment of many diseases The different biologic houses place on the market ampules varying in size from 1 cc. to 20 cc. A large number of these ampules are rubber capped and the contents must be aspirated by a syringe and needle. It is undoubtedly an awkward procedure. One must fill the syringe with air and work the plunger back and forth in order to withdraw the required amount for the injection This usually produces a foam in the barrel of the syringe which is annoying



Ampule needle

I have been in the habit of injecting a small hypodermic needle into the rubber cap at the same time that I wish to withdraw the fluid by the syringe and needle. This second hypodermic needle acts as an air vent. The necessary amount of fluid can then be withdrawn without effort and waste

It occurred to me that a special ampule needle might be devised containing the air vent welded to the needle shaft A number of these needles have been made up and their practicability has been tried out for several months The needle tubing that is used as an air vent has been placed far enough back on the Luer needle so that it does not cause any inconvenience when the injection is given intravenously or subcutaneously During the last few months the pediatricians have been using large amounts of human and convalescent blood serum in the treatment of measles The serum is put up by local laboratories in rubber-capped ampules of 10 cc each This needle affords a considerable saving of time in emptying the ampules, as well as facility in the administration of the serum.

Connell Building

---

[5] Brehm Wayne and Weirauk H V Separation of the Symphysis During Labor Am J Obst. & Gynec 15 187 191 (Feb) 1928

[6] Beach Ralph Traumatic Separation of the Symphysis Pubis Am J Obst. 175 203 (Feb) 1917

[7] Boorstein S W Separation of the Symphysis Pubis with a Report of Six Cases Am. J Obst 13 345 351 (March) 1927

[8] Allen J M Report of a Case of Separation of the Pubic Symphysis in a Forceps Delivery and the Treatment Employed Am. J Obst. 175 808 (May) 1917

[9] McNamara S J Wiring Through the Obturator Foramen for Symphysis Pubis Separation Surg Gynec Obst. 23 625 (Nov) 1916

* These ampule needles were made up for me by the firm of William Alfred Lewis 38-40 West Thirty Third Street New York.

TECHNIC OF CHOLECYSTOGASTROSTOMY *

J Tate Mason, M D Seattle

The method of diverting the contents of the gallbladder into the gastro-intestinal tract described here has been used by us for several years I feel that it is the simplest procedure possible when the necessity of creating a new passage for bile is evident. It is possible to obtain a certain amount of muscular control between the gallbladder and the stomach by separating the muscles of the stomach with a hemostat. For this reason as well as on account of the inaccessibility of the duodenum I have not done a cholecystoduodenostomy for years It is remarkable what beneficial results are obtained and how long these patients continue relatively well

OPERATIVE PROCEDURE

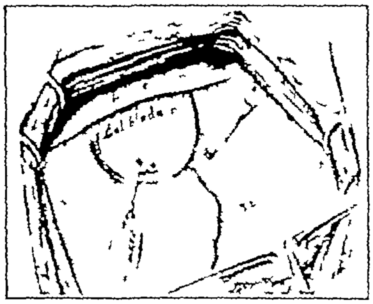


Fig 1 —Position of incision

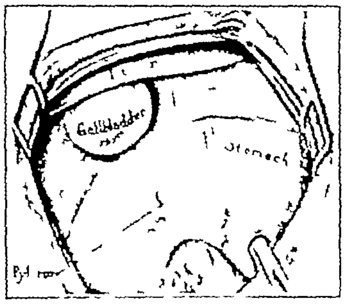


Fig 2 —Hemostat enlarging the opening in stomach.

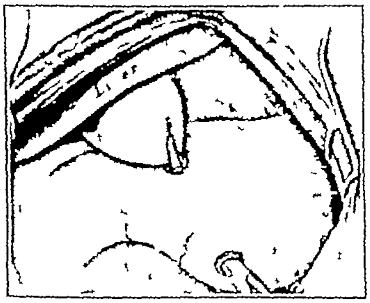


Fig 3 —Fundus being pulled through the opening into stomach

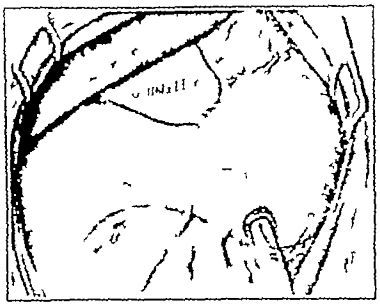


Fig 4 —Fundus of gallbladder opened by scissors

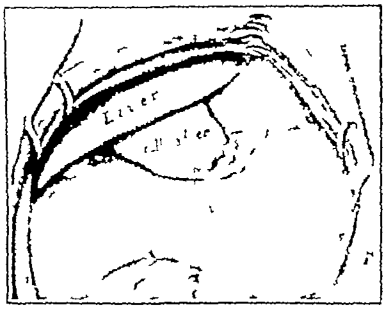


Fig 5 —Closure of the initial incision.

A small incision 1 cm long is made on the anterior surface of the stomach wall near the pyloric end about 2 cm. from the greater curvature (fig 1) The incision is extended into the cavity of the stomach and a curved clamp is inserted, directed upward and laterally to a point near the lesser curvature, level with the gallbladder It is gently pushed through the mucosa and the muscular fibers of the stomach wall. If the gallbladder is so distended that it is dangerous to grasp it with a hemostat, aspiration with a small needle is first made

The blades of the hemostat are opened gently and turned until the opening in the stomach is large enough to admit the fundus of the gallbladder This permits a sphincteric action of muscles around the anastomosis (fig 2)

The fundus of the gallbladder is grasped and pulled through the opening into the stomach It is fixed with a single row of waxed silk sutures (fig 3) A pair of scissors is passed through the lower opening and the fundus of the gallbladder opened (fig 4) A small amount of fat from the gastrocolic omentum reinforces the anastomosis and the initial incision is closed (fig 5)

1101 Terry Avenue

---

* From the Mason Clinic.

Malta Fever—American physicians gave little thought to Malta fever until Col C F Craig of the U S Army in 1905 reported a case in a nurse who had been engaged in nursing soldiers in the Washington D C hospitals This was the first case reported in the United States—Hines E A Some Observations on the First Reported Cases of Malta Fever in South Carolina *J S Carolina M A* December 1929

ANEURYSM OF THE ASCENDING PALATINE ARTERY
CHRONIC COUGH RELIEVED BY LIGATION

Harold Brunn M D, and A. Lincoln Brown M.D, San Francisco

A review of the available literature fails to provide the report of a single case of nontraumatic aneurysm of the external carotid artery or any of its branches A few reports of traumatic aneurysms, particularly due to gunshot injuries are noted, especially during the war period. We therefore believe the case reported here of sufficient interest to be recorded

The patient was first seen by one of us (A. L. B) late in December, 1928. The following history was obtained at that time

History—E. B J, a white man aged 64, an American, complained of cough and malaise. He had an incessant, nonproductive cough of five days' duration, which was worse at night and was aggravated by lying down, but also occasionally woke the patient when asleep while propped up in almost a sitting posture. The patient expectorated two masses of blood tinged sputum on the morning of examination Otherwise the cough produced only a frothy sputum resembling saliva There was also moderate pain, stabbing in character, in the lower left portion of the chest, which was aggravated by coughing or turning The patient had been confined to bed for twenty-four hours before examination

The family history was essentially negative The patient had been married twenty-seven years His wife was living and well except for essential hypertension. She had no children, there were no miscarriages

The patient slept from six to eight hours in bed he suffered from insomnia. He had taken a minimum of 5 grains (0 3 Gm) of barbital daily for the past ten years usually at night He used alcohol occasionally and moderately, and tea, rarely He drank two or three cups of coffee daily and smoked from eight to ten cigars daily, and an occasional cigaret

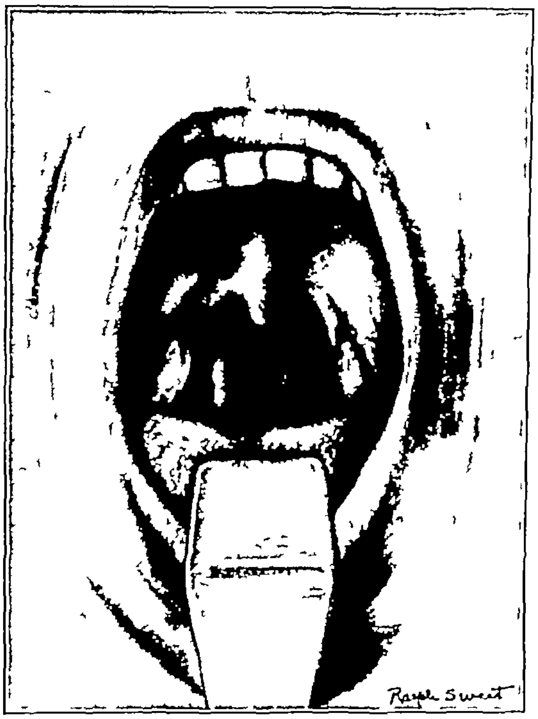
He was born and lived practically his entire life in San Francisco His general health was always good He did not remember having any serious illnesses He never had pneumonia diphtheria whooping cough, influenza, pleurisy tuberculosis or tonsillitis There was no association with tuberculosis

He had had frequent head colds and attacks of sore throat, eight or ten yearly, for the past fifteen years and had been treated by several throat specialists for laryngitis and bronchitis These colds' were associated with paroxysmal nonproductive cough similar to that of the present illness, only partially relieved by steam inhalations and various codeine-containing cough mixtures The tonsils had *not* been removed

The patient had a right inguinal herniotomy in 1925 under local anesthesia without complications and he had had several carious teeth extracted during the past ten years He had not had any accidents

Physical Examination—The patient was well developed and well nourished He was in no acute distress, resting quietly in bed with the head elevated on three pillows, coughing paroxysmally and raising bits of frothy sputum.

The skull was normal in contour, and there was no tenderness The scalp was clean and without scars The hair was normal in amount, distribution and texture The eyes showed beginning arcus senilis Reaction to both light and distance was poor The right pupil was slightly smaller than the left There was no photophobia, diplopia, nystagmus or exophthalmos There was no gross disturbance of vision The fundi were negative except for moderate tortuosity of the retinal vessels Examination of the ears did not reveal any mastoid tenderness There was no gross disturbance of hearing There was marked deviation of the nasal septum to the right with partial obstruction on that side The teeth were in poor condition but were being cared for, the tongue protruded in the midline without tremor There was no enlargement or exudate of the tonsils noted The pharynx was inflamed and there was some posterior nasal discharge. The adenoids were not hypertrophied. The patient's voice was slightly hoarse, but this was usual for him The vocal cords were thickened and inflamed, and the membranes were beefy red The thyroid glands were not palpably enlarged. There were no bruits, thrills or abnormal pulsations, and there was no stiffness or tracheal tug present, but there were slight pea sized anterior cervical nodes



Aneurysmal dilatation on right posterior nasal pharyngeal wall before ligation of right external carotid artery

The thorax was symmetrical with equal expansion on the two sides, it was normal in size and shape Respirations were 20 and somewhat shallow There were no abnormal pulsations

The heart action was regular with clear sounds and without murmurs The base measured 5 5 cm. The right broad diameter was 2.5 cm., and the left broad diameter, 9 cm The apex impulse was seen and felt in the fifth interspace in the nipple line

The radial pulses of the peripheral vessels were regular, equal and synchronous Marked sclerosis of the brachial and radial vessels was present, and the temporal vessels were moderately tortuous and sclerosed. The blood pressure was 138 systolic and 90 diastolic

Numerous harsh moist rales were scattered throughout both lungs At the left base posteriorly a faint pleural friction rub was heard. On the abdomen was the scar of the herniotomy The liver edge was smooth, and palpable 1 cm below the costal margin There were no masses, tenderness or spasm Rectal examination showed the sphincter normal in tone The prostate showed moderate uniform hypertrophy The skeletal system was essentially normal The legs did not reveal any varicosities or ulcers Knee jerks were active and equal The achilles jerks were normal, and there was a normal Babinski and Romberg response Neuromuscular examination did not reveal any areas of anesthesia, paresthesia or hyperesthesia The temperature was 99.2 The weight was 176 pounds (80 Kg)

Laboratory Observations—The blood Wassermann reaction with cholesterol antigen and with plain antigen was negative. The red blood cells numbered 4,762,000, with hemoglobin 85 per cent by the Tallqvist method A stained specimen was essentially normal The white blood cell count was 7,200 with 64 per cent neutrophils, 26 per cent small mononuclears, 8 per cent large mononuclears and 2 per cent eosinophils The urine was clear, light amber and alkaline, with a specific gravity of 1 022, there was no sugar or albumin A roentgenogram of the chest showed marked widening of the thoracic aorta with generalized cardiac enlargement.

Treatment and Course—The immediate treatment was symptomatic, consisting of codeine cough mixtures, steam inhalations and medical diathermy to the chest Within a week the chest signs and symptoms had cleared up but the irritative cough persisted It now happened that the throat was examined while the patient was turned on his left side There was then noted for the first time on the right posterolateral pharyngeal wall a distinct pulsating tumor, bean sized, which protruded into the pharyngeal cavity about three-eighths inch with each pulsation. The rate corresponded to that of the heart With the patient in the erect position or turned to the right the tumor was barely visible, which fact probably accounts for its having previously passed unnoticed The remainder of the physical examination was essentially as noted There was no pulsation, mass or bruit in the neck, no headache and no external differences in vascular efficiency to be observed when the vessels on the right side of the head and neck were compared with those on the left When the patient was questioned again, it was determined that about twenty years before he had received a thorough course of treatment for what was probably a syphilitic infection

He was now advised that if the cough persisted it might be advisable to ligate the right external carotid artery in the hope that this aneurysmal dilatation was the inciting cause of the chronic cough The next three weeks was spent in a warm, dry climate but the cough persisted Reexamination showed that the tumor had enlarged to about four times its original size but that it was still visible only through the buccal cavity The rapid growth of the tumor gave rise to fears of possible rupture. Therefore and with the hope that the cough might be allayed, it was decided to perform a ligation of the external carotid artery, which operation was done by one of us (H B), Feb 18, 1929

Operation and Result—Under cervical nerve block anesthesia obtained with about 60 cc. of 1 per cent procaine hydrochloride solution, an incision 5 cm in length was made parallel to the anterior border of the right sternocleidomastoid muscle beginning at the level of the angle of the jaw The fascia was separated by sharp dissection, the posterior belly of the digastric muscle was divided and the great vessels of the neck were exposed The external carotid was freed for a distance of 4 cm No aneurysmal dilatation was made out However, compression of this vessel caused a cessation of the pulsation observed in the pharynx and the subsidence of the tumor The external carotid was now doubly ligated with linen, 1 cm above the bifurcation. The right facial, lingual and superior thyroid arteries were now ligated to prevent the engorgement of the tumor by means of this profuse collateral circulation The complete collapse of the tumor as seen through the mouth was definitely determined before closing The fascia was approximated with plain catgut sutures, with Michel clips to the skin. The patient returned to bed in excellent condition.

The postoperative course was uneventful and, one week after the operation, the patient went home At that time the tumor in the pharynx was still collapsed, the right temporal artery was pulseless, and there were no visible or symptomatic circulatory disturbances in any portion of the territory supplied by the external carotid One month later the general health was good There was no pulsation or mass to be seen on the inside of the throat The wound and subcutaneous thickening were gradually reducing in size and were not tender Pulsation was not noted internally The coloration of the face was bilaterally uniform No pulsation could be made out in the right superior temporal artery The patient had not had any attacks of coughing since the operation

This status persists to date, more than nine months after operation

COMMENT

There is little doubt that we were dealing here with an aneurysmal dilatation of one of the branches of the right external carotid artery Before operation it was thought that possibly the ascending pharyngeal artery was involved but the operative results ruled this out so that the lesion must be considered to have been of a terminal branch of the external maxillary artery, i e the ascending palatine artery

The etiology is likewise somewhat obscure First of all there is the suggestive syphilitic history Secondly a generalized vascular sclerosis was noted The third factor is cough Did the chronic cough aid in the production of the tumor or was the tumor the irritating factor producing the cough? A vicious circle may well have been established

In spite of these uncertainties this case is presented because of the apparent rarity of aneurysms of the external carotid artery or its branches and because ligation of such an aneurysm relieved an otherwise intractable cough

384 Post Street—490 Post Street.

Council on Pharmacy and Chemistry

NEW AND NONOFFICIAL REMEDIES

The following additional articles have been accepted as conforming to the rules of the Council on Pharmacy and Chemistry of the American Medical Association for admission to New and Nonofficial Remedies A copy of the rules on which the Council bases its action will be sent on application

W A Puckner Secretary

DIPHTHERIA TOXOID (See New and Nonofficial Remedies, 1929 p 368)

The National Drug Co Philadelphia

Diphtheria Toxoid —Prepared from seven day cultures of the diphtheria bacillus that yield a toxin having an L+ dose of not less than 0 25 cc the antitoxin used in the preparation is obtained from goats The toxin is treated with formaldehyde until its toxicity is so reduced that five maximum human doses will cause no local or general symptoms of diphtheria poisoning when injected subcutaneously into guinea pigs The product is tested for antigenic potency by injection subcutaneously of 0 5 cc. into each of at least ten guinea pigs weighing between 270 and 320 Gm at the end of thirty days the animals are injected subcutaneously with five minimum lethal doses of a stable diphtheria toxin 80 per cent of the animals must survive. It is marketed in packages of three vials (one immunization treatment) each containing 0 5 cc. of the toxoid in packages of one vial (fifteen immunization treatments) containing 22 5 cc of the toxoid in packages of forty five vials (fifteen immunization treatments) each containing 0 5 cc. of the toxoid The immunization treatment consists of three doses of 0 5 cc each of the toxoid given at intervals of three weeks

SCARLET FEVER STREPTOCOCCUS ANTITOXIN (See New and Nonofficial Remedies 1929 p 350)

Cutter Laboratory Berkeley Calif

Scarlet Fever Streptococcus Antitoxin-Cutter —It is prepared by the method of Drs Dick under U S patent 1 547 396 (July 28 1925 expires 1942) by license of the Scarlet Fever Committee Inc The serum is concentrated by a modification of the Banzhaf method Marketed in packages of one syringe containing 2 000 units (prophylactic dose) and in packages of one syringe containing 6 000 units (therapeutic dose)

TYPHOID VACCINE (See New and Nonofficial Remedies, 1929 p 378)

H K. Mulford Company Philadelphia

Typho-Bacterin Mixed (Triple Vaccine TAB) (See New and Nonofficial Remedies 1929 p 380) —Also marketed in packages of thirty 1 cc vials (M 195 5) being ten immunizations of three doses each the first dose containing 500 million killed typhoid bacilli and 250 million each of killed paratyphoid A and paratyphoid B bacilli and the second and third doses each containing 1 000 million killed typhoid bacilli and 500 million each of killed paratyphoid A and paratyphoid B bacilli

REPORTS OF THE COUNCIL

The Council has authorized the publication of the following report W A Puckner Secretary

AMPOULE NO 61 SODIUM SALICYLATE 15½ GRAINS, AMPOULE NO 59 SODIUM IODIDE 15½ GRAINS, AMPOULE NO 66X SODIUM SALICYLATE, SODIUM IODIDE 15½ GRAINS EACH, AMPOULE NO 66 SODIUM SALICYLATE, SODIUM IODIDE AND COLCHICINE, AND AMPOULE NO 50 IRON AND ARSENIC (IRON CACODYLATE) 1 GRAIN NOT ACCEPTABLE FOR N N R

Among the Ampoule Preparations for Intravenous Use marketed by the Lakeside Laboratories Inc Milwaukee are the following Ampoule No 61 Sodium Salicylate 15½ grain Ampoule No 59 Sodium Iodide 15½ grains Ampoule No 66X Sodium Salicylate Sodium Iodide 15½ grains each, Ampoule No 66 Sodium Salicylate Sodium Iodide and Colchicine and Ampoule No 50 Iron and Arsenic (Iron cacodylate) 1 grain

The Council in reporting on Some of Loeser's Intravenous Solutions (The Journal April 16, 1921 p 1120), stated

> The Council continues to hold that intravenous medication generally, is not as safe as oral medication even with relatively harmless substances (a fact again illustrated by the results of Hanzlik and Karsner 1920 *Journal Pharmacology and Experimental Therapeutics* **14,** 379) and that it does not give improved clinical results except under rather narrowly confined circumstances—namely if the drug undergoes decomposition in the alimentary tract, if it is not absorbed if it cause serious direct local reaction or if time is an urgent element Each intravenous preparation for which advantage over oral administration is claimed directly or by implication must be examined from these points of view
>
> The Council has recognized intravenous preparations which satisfied these requirements It is evident however that hexamethylenamin, sodium iodid and sodium salicylate do not When given orally they do not undergo material decomposition in the digestive tract, they are rapidly absorbed, they cause no direct local reaction and in the conditions in which they are used the hour or so which is required for absorption is immaterial especially as they are used continuously for some time Especially objectionable are the fixed proportion mixtures of sodium iodid with sodium salicylate and with hexamethylenamin. The dosage of all three drugs has to be adapted to individual conditions This is impossible when giving them in fixed proportions

Since publication of this report no evidence in favor of the routine intravenous administration of sodium salicylate or of sodium iodide has been brought forward[1]

The objections of the Council to the intravenous administration of drug mixtures in fixed proportions applies of course to those mixtures of this firm which are listed in this report Ampoules No 50 Iron and Arsenic (Iron Cacodylate) is unacceptable because the indefinite term iron and arsenic rather than the descriptive name iron cacodylate is used as the name because recommendations for the routine intravenous use of iron are not warranted and because ferric cacodylate presents an irrational and useless method of the administration of iron and arsenic (Reports Council on Pharmacy and Chemistry 1920 p 62)

The Council declared Ampoule No 61 Sodium Salicylate 15½ grains Ampoule No 59 Sodium Iodide 15½ grains Ampoule No 66X Sodium Salicylate Sodium Iodide 15½ grains each Ampoule No 66 Sodium Salicylate, Sodium Iodide and Colchicine and Ampoule No 50 Iron and Arsenic (Iron cacodylate) 1 grain unacceptable for New and Nonofficial Remedies because recommendations for the routine intravenous administration of sodium salicylate and sodium iodide are not warranted and because the administration of sodium salicylate and sodium iodide of sodium salicylate sodium iodide and colchicine in fixed proportion and of iron and arsenic in the form of ferric cacodylate whether intravenously or otherwise is irrational

---

[1] On the contrary experienced physicians have reported that they consider it no practically feasible in many cases to give a sufficient number of intravenous injections of sodium iodide to meet the need of some patient

THE JOURNAL OF THE
AMERICAN MEDICAL ASSOCIATION

535 North Dearborn Street Chicago, Ill.

Cable Address Medic, Chicago"

Subscription price Seven dollars per annum in advance

Please send in promptly notice of change of address giving both old and new always state whether the change is temporary or permanent Such notice should mention all journals received from this office Important information regarding contributions will be found on second advertising page following reading matter

SATURDAY, JANUARY 4, 1930

THE PREMATURE INFANT

The premature infant is subject to malformation and to intra-uterine infection, such as syphilis, just as is the full-term infant These conditions may be a cause, but not the result, of prematurity They may be the cause of abnormality or death but the reaction of the premature infant to them differs in no way from that of the full-term child Its incomplete development at the time of birth causes the premature infant to react differently from the normal infant to its external environment Because of incomplete development of the nervous system, the temperature regulating mechanism does not have the automaticity of action that characterizes this mechanism at a later period The premature infant is therefore extremely sensitive to external thermal conditions and reacts to a temperature lower than that of the normal body in a manner deleterious to itself It is, to a certain degree at least, a poikilothermic rather than a homothermic organism Incomplete preparation for independent existence starts the premature infant in life with metabolic requirements that are difficult to meet and that make its alimentation no easy task Incomplete development of the reflexes probably renders the premature infant more than usually susceptible to respiratory infection, deficient expansion of the lungs probably being an added factor in such infection Detrimental reactions to external temperature, special nutritional requirements, and susceptibility to infection, all of which are the result of the state of prematurity, render precarious the premature infant s slender hold on life These physiologic or functional abnormalities, which are peculiar to the premature infant because of its prematurity, can be overcome in large measure by means directed toward this end, such as the maintenance of constant and proper temperature and humidity of the atmosphere, careful nursing, and breast-milk feeding Hess and Chamberlain[1] have described the application of such measures in the hospital properly equipped for the care of premature infants, and have analyzed the maternal, fetal and postnatal factors that affect the viability of such infants In 266 admissions to the premature infant station of the Sarah Morris Hospital for Children, the mortality was 40 8 per cent, indicating the importance of factors other than those that can be combated by proper care

Glaser,[2] who studied a series of 100 infants from the same source as that of Hess and Chamberlain, directed his attention to changes in the cerebrospinal fluid The high mortality of 81 per cent in this series was due to the inclusion of as many cases as possible of intracranial hemorrhage Necropsy was done in seventy (79 per cent) of the eighty-one infants that died, and it is on these seventy premature infants, from whom cerebrospinal fluid was obtained during life or immediately after death, that Glaser's study was based Twenty-six, or 36 per cent, revealed macroscopically evident subarachnoid or subpial hemorrhage The cerebrospinal fluid was grossly bloody in 73 per cent of these The blood-free fluid of the seven infants with hemorrhage was distinctly yellow In 31 per cent of the forty-two infants without macroscopic evidence of intracranial hemorrhage, the fluid was grossly bloody Sixty-two per cent of the fluids that on gross examination were free from blood were found on microscopic examination to contain erythrocytes Of the total seventy cases, only eighteen, or 26 per cent, failed to show blood in the spinal fluid, most of these negative fluids were yellow The absence of blood in the cerebrospinal fluid of 27 per cent of twenty-six infants in whom necropsy revealed gross hemorrhage indicates that subpial hemorrhage may be present and may fail to manifest itself by free blood in the fluid because the blood is confined beneath the pial membrane The presence of erythrocytes in the fluid of 73 per cent of forty-two infants in whom necropsy failed to disclose gross hemorrhage is evidence that the finer vessels of the pia-arachnoid may be injured without the production of grossly recognizable hemorrhage Xanthochromia, a yellow coloration of the cerebrospinal fluid, received particular attention in the study of Glaser Only five of fifty-two water-clear cerebrospinal fluids of premature infants were absolutely colorless These colorless fluids came from infants aged 60 days or over The color was deepest from 2 to 14 days of age All of the yellow fluids gave a negative benzidine reaction for hemoglobin Half of forty-six yellow, water-clear, benzidine-negative fluids gave a positive indirect van den Bergh reaction From these results it is apparent that half of the fluids contained a pigment that is not hemoglobin, since the benzidine reaction was negative, nor is it bilirubin, since the van den Bergh reaction was negative It is probably an intermediate hemoglobin derivative From the frequency with which blood and its derivatives occur in the cerebrospinal fluids of premature infants, Glaser concludes that some degree of intracranial hemorrhage is, so to speak physiologic But the fact that subpial hemorrhage was of such an extent as to cause the death of 37 per cent of premature infants examined post mortem establishes the importance of this pathologic process as a menace to the life of the prematurely born

---

[1] Hess J H and Chamberlain I M Premature Infants A Report of Two Hundred and Sixty Six Consecutive Cases Am J Dis Child 34 571 (Oct.) 1927

[2] Glaser Jerome The Cerebrospinal Fluid of Premature Infants with Special Reference to Intracranial Hemorrhage and Pigmentation, Am J Dis Child. 36 195 (Aug) 1928

Clein,[3] who also worked with the material of the premature infant station of the Sarah Morris Hospital, correlated the antemortem clinical symptoms with the postmortem pathologic observations Of his series of 102 patients admitted consecutively, forty-eight died, a mortality of 47 per cent, which is a little higher than the death rate of the larger series reported by Hess and Chamberlain The most striking and frequent symptom in the infants who died was cyanosis, of which four types are recognized by Clein cyanosis that is continuous from the time of its appearance, usually at birth, intermittent cyanosis, the attacks occurring usually during the first to third days of life, and again from the seventh to eighteenth day if the infant lives that long, terminal cyanosis, and sporadic attacks for which a definite cause, such as vomiting, coughing, or choking during feeding, can usually be found Eighteen, or 50 per cent, of the infants examined post mortem had intracranial hemorrhage situated beneath the tentorium, usually over the superior surface of the cerebellum and in the cerebellopontile angle In all of these, intermittent cyanosis had been the striking symptom This symptom was noted in only one infant who did not have infratentorial hemorrhage, and it was not seen in the infants who lived In nine of eighteen infants with infratentorial hemorrhage there was also supratentorial hemorrhage, usually localized over the parietal lobes In three infants with intracranial hemorrhage, the latter was entirely supratentorial, none of these infants had exhibited intermittent cyanosis during life Continuous cyanosis, when not due to a congenital heart lesion, which was the chief cause of death in only one infant, was due to pulmonary atelectasis, which was held to be the major pathologic lesion in 7 per cent of the cases Otitis media, with or without mastoiditis, was considered the chief lesion in 17 per cent The relation of this process to diarrhea vomiting and fever is emphasized by Clein as it has been by others in young full-term infants It is probably a terminal infection, resulting from a poor nutritional state and low resistance When a second series of attacks of cyanosis occurred from the seventh to the eighteenth day in an infant that had had intermittent cyanosis during the first three days of life, infratentorial hemorrhage was found associated with infection

From the work of Hess and Chamberlain, of Glaser and of Clein, it is apparent that the most important factors which endanger the premature infant s hold on life are the pathologic functioning that is the result of the incomplete development of the infant, intracranial hemorrhage and pulmonary atelectasis The frequency and importance of these factors vary inversely with the intra-uterine age of the infant at the time of birth the more premature the infant the more frequently do these factors operate as causes of death They are the expressions of prematurity and are its principal pathologic manifestations After them come nonsyphilitic infections, to which the premature infant is probably somewhat more liable than is the normal full-term infant, and congenital syphilis which may be a cause of prematurity and therefore relatively more frequent than in full-term infants After all of these come the malformations and maldevelopments

INDUSTRIAL MEDICINE

Bernardino Ramazzini, in the years near 1690, laid the foundations of industrial medicine and has become its patron saint In his Diseases of Artificers and Tradesmen,' published in 1700, he considered in forty-three chapters the occupational ills of metal workers alchemists, glassmakers, potters, painters, dyers, tanners, bakers, millers, masons, surgeons, barbers wrestlers and learned men As Legge [1] tersely states, Ramazzini omits little save the hazards of steamship building and the manufacture of high explosive shells Confronted with the ravages of small numbers of simple intoxicants, he wrote of mercury, for example

> 'Tis well known what dismal Plagues are inflicted by Quicksilver upon Goldsmiths, and chiefly those who are employed in Gilding Silver or Brass Work For as this Gilding can't be performed without Amalgamation (i e the Corrosion of the Mettal by Mercury), so when they afterwards come to dislodge this Mercury by Fire, tho they turn away their Faces they can't possibly avoid the receiving some poysonous Steams at the Mouth and accordingly we find that this sort of Workmen do quickly become Asthmatick, Paralytick and liable to Vertigo s, and their complexion assumes a dangerous Ghostly Aspect

Today the complex chemical intoxicants are so numerous that they may not even be enumerated Indeed, new chemicals and new hazards appear constantly The far removed day of Ramazzini may be emphasized no better than in his own words

> If we consider what a vast difference there is between the Europeans and the Americans, and other barbarous nations of the New World, we can't but be sensible that mechanik arts have contributed very much towards the civilising of mankind

Industrial medicine of the present day is concerned with the fact that the available energies of the workman should be so conserved, so renewed so applied and so protected that work may be performed with continuity and reasonable regularity, over a long work life expectancy, with advantage alike for himself and his employer The foremost objectives of industrial medicine are (1) to fit every person to types and quantities of work according to his ability to perform such work continually without undue impairment, without injury to himself or his fellow workmen, and with profit to himself and his employer, (2) to procure and maintain fitness for work through efforts applied to the worker as an individual, to groups of workers, and to the work environment, (3) to educate the worker to a comprehension of the value and significance of physical and mental well being and, in particular, of personal hygiene and accident prevention, and (4) to reduce all loss of time, absenteeism and short work spans in industry the cause of which may be related in any way to health

---

[3] Clein A W Premature Infants A Clinical and Pathologic Study Am J Dis Child 37 751 (April) 1929

[1] Legge T M Industrial Diseases Under the Mediaeval Trade Guild J Indust. Hyg 1 475 (Feb) 1920

With these boundaries, much so-called industrial medicine is revealed as quite beyond the legitimate field Medical care of entire communities in mining areas or kindred enterprises, through contract arrangements, with the family as the unit, may lead to organized or socialized medical care but it is not within the scope of industrial medicine The physician who practices in an industrial community and cares for cases originating in industries may render appropriate care for these industrial cases and yet meet most meagerly the requirements of industrial medicine at its best The physician lending his standing to the confounding of compensation cases in order that a casualty company's experience may be continually profitable may deal with industrial cases, but he too is far afield from industrial medicine The layman, feverish in his desire to turn the bad by-products of human impairment in industry into profit, may organize, incorporate and employ physicians He administers industrial medicine only when through skilled industrial physicians he meets the objectives earlier set forth Seldom, if at all, do these activities on the fringes of acceptable industrial medicine conform to the most desirable provisions within that specialty of medicine

The early craft guilds were the only friendly benefit and sick associations of their times The guilds cherished (1) honest, thoroughgoing workmanship, and (2) the protection of their sick Thus, early industrial medicine was purely "fraternal" Changing work systems now lead to the charge that industrial medicine is purely "paternal" Industrial medicine should be neither It must deal with the worker as a producing unit and not as a social unit It centers about the factory and not the home Its activities partake of the practice of both public health and curative medicine, and it deals with workers as individuals and in groups Intelligent, constructive selfishness is the industrial point of view for this form of medicine, but before such measures may be profitable to industry they must be applied to and profit the worker Conceived in selfishness, industrial medicine culminates in humanitarianism

The ramifications of our industrial civilization have made the study and organization of industrial medicine a necessity The need is great for organized medicine (1) to mark the just and proper domain of acceptable industrial medicine, (2) to stimulate a demand for the truly qualified industrial physician and (3) to limit industrial medicine wholly to the boundaries set forth If industrial medicine becomes merely a pathway to general care of all the sick by poorly educated, low salaried medical "hacks" it will defeat the very need by which it came into being

Current Comment

SPECIFICNESS OF IMMUNE REACTIONS

If the chemical nature of specific groups or of unique details in structure which confer on proteins their ability to act as specific antigens could be determined, it would mark an advance of fundamental importance in the science of immunology Although our knowledge of the protein molecule is at present wholly inadequate for this purpose, important information may be obtained by observing changes in specificity resulting from the formation of protein derivatives of definite structure The earlier attempts in this field resulted for the most part in the production of ill defined derivatives of unknown structure Recently Landsteiner and van der Scheer [1] prepared compounds of horse and chicken serum with the optical isomers of tartaric acid and found that these derivatives, when injected into rabbits, produced antiserums which differentiated specifically between the dextrotartaric and the levotartaric acid combined with the protein Similar results were obtained by Avery and Goebel,[2] working with compounds of serum globulin and egg albumin with identical derivatives of dextrose and of galactose In both series of experiments, antibodies were produced which reacted specifically with the simple radicals used, regardless of the type or species of protein with which they were combined In both cases, also, specific antiserums were obtained which differentiated between stereo isomers differing from one another only in the arrangement of the various groups in the molecule, in space The results obtained are far-reaching in importance In the first place, they emphasize again the fact, previously established especially by Landsteiner, that the specificity of a large colloidal molecule or complex may be determined entirely by a comparatively small reactive group in that molecule In this connection, recent work on enzymes indicates that here, too, the specificity of the colloidal complex may be determined by a small reactive group The nature of the simple compounds used in both series of experiments indicates that the spatial arrangements of the groups in the reactive part of the molecule may determine the specificity of the entire complex, many hundred times its own size This is especially striking in the experiments of Avery and Goebel, in which the compounds of dextrose and of galactose utilized differed from one another only in the relative positions in space of the H and OH groups on a single carbon atom. The conclusion seems inevitable that the specificity of immune reactions may be due not only to a comparatively small reactive part of the colloidal antigen but also to a definite arrangement in space of the groups comprising this reactive part of the complex injected. Notions of the chemical nature of antigens must also be revised to include compounds of this sort which are chemically identical but immunologically specific as the result of different orientations in space of groups in the reactive part of the colloidal molecule.

---

[1] Landsteiner K and van der Scheer J Serologic Differentiation of Steric Isomers (Antigens Containing Tartaric Acids) Second Paper J Exper Med **50** 407 (Oct) 1929

[2] Avery O T and Goebel W F Chemo-Immunological Studies on Conjugated Carbohydrate Proteins J Exper Med **50** 533 (Oct) 1929

EXCRETION OF BARBITAL

In his presidential address on the dangers of insomnia, delivered before the section of psychiatry of the Royal Society of Medicine last year, Sir Maurice Craig[1] favored the prolonged use, when necessary, of drugs of the barbital group, or barbitone group as it is called in Great Britain. He believes that, when given in small doses, these act by protecting a weakened inhibition, and in his experience they may be taken for years without producing deleterious effects. This view receives some confirmation from recent experimental work in the University of Alberta.[2] Hypnotic doses of barbital (up to 25 per cent of a fatal dose) were administered to four cats over a period of ten weeks. At the end of this time the barbital produced just as much depression as when it was administered for the first time. A cumulative effect appeared only during the first few days of administration. Subsequent observations showed that this was due to a lag in excretion. In the second week the excretion increased and thereafter no cumulative effect was observed. Some psychiatrists insist that sedative drugs have no place in psychiatry. Directors of psychopathic institutions complain that many patients are admitted in a state of toxic delirium for which they have to be treated before the underlying psychosis can receive attention. Such cases, it must be admitted, are often due to self-medication. Sir Maurice Craig argues that, if physicians would be more generous in prescribing suitably for such patients, self-medication would be less often attempted. Tillotson[3] believes, however, that in certain conditions—manic-depressive insanity, constitutional psychopathic inferiority and psychoneuroses—there is a predisposition to habit formation and that to such patients these drugs should never be administered. Here is a reasonable difference of opinion which can be settled only by further observation. In the meantime it is clear that careful attention should be given to the class of patient for whom barbital is prescribed and that in writing prescriptions the use of trade names should, as far as possible, be avoided.

ABSCESS FROM SWALLOWED BONE

Injury to the intestinal wall from swallowed fishbones may not be as rare as has been supposed. Although reference to such injuries is seldom found in the literature, three cases treated within a period of nineteen months have recently been reported.[1] In two cases the fishbone was recovered from within an intra-abdominal abscess and in the third case, although the swallowed fishbone had been removed from the rectum by the patient, perforation had already occurred necessitating an operation for the resulting abscess. Perforation is more common in the large than in the small intestine, perhaps because of its fixed position, thinner sacculated wall, and vigorous peristaltic movements. Dr. Bearse remarks that acute symptoms are usually lacking since perforation takes place slowly. The history is usually one of gradually increasing pain and tenderness, with the development of a mass. There is no complaint of obstruction, but when the rectum has been perforated defecation may be painful. The patient may or may not recollect having swallowed a fishbone. In the latter case it may be impossible to make a sure diagnosis, for little if any shadow of a fishbone is thrown by the roentgen ray.

FACTORS AFFECTING THE SERUM CALCIUM

Investigations of such physiologic phenomena as the acid-base balance of the body and the neutrality regulation of the blood indicate the complexity of the reactions involved. The fluids of the organism normally represent a sort of equilibrium in which numerous determining factors are involved. A shift in the concentration of any one of them may occasion compensatory readjustments involving several other factors. The "steady states" of the body represent the results of an interplay of functions whereby "homeostasis,"[2] as Cannon designates the condition, is brought about. An interesting instance of this has just been reported by Peters and Eiserson[3] of the Yale University School of Medicine. They found that the concentration of calcium in the serum varies directly with the concentration of protein and inversely with the concentration of inorganic phosphorus. It is therefore impossible to interpret serum calcium variations accurately unless protein and inorganic phosphorus are simultaneously determined. A low calcium value need not represent any primary disturbance in calcium metabolism unless the values for the other components referred to are taken into consideration. A serum calcium content low in proportion to the protein and phosphorus is, however, significant. Thus the Yale clinicians have observed in certain kidney disorders that when calcium is found extremely low without important protein or phosphorus abnormalities the calcium reductions are due to disturbances of calcium metabolism and the mechanism of calcification and not to the renal disease itself Such hypocalcemias are usually encountered in children, who are more prone to such disorders of calcification than adults The interpretation of analytic data regarding the make-up of the blood is thus becoming more difficult and exacting

---

[1] Craig, Maurice: A Survey of Some Conditions Conducive to Mental Disturbance with Suggestions as to Their Treatment, Proc. Roy. Soc. Med. **22**: 197 (Dec.) 1928.

[2] Eddy, N. B.: The Effect of the Repeated Administration of Diethyl Barbituric Acid and of Cyclohexenylethyl Barbituric Acid, J. Pharmacol. & Exper. Therap. **37**: 261 (Nov.) 1929; The Excretion of Di-Ethyl Barbituric Acid During Its Continued Administration, ibid. **37**: 273 (Nov.) 1929.

[3] Tillotson, K. J.: The Abuse of Drugs in Certain Psychopathic States with Reports of a Few Cases, New England J. Med. **200**: 990 (May 9) 1929.

[1] Bearse, Carl: Fishbones as a Cause of Intestinal Perforation, New England J. Med. **201**: 885 (Oct. 31) 1929.

[2] Physiologic Homeostasis, editorial, J. A. M. A. **93**: 1385 (Nov. 2) 1929.

[3] Peters, J. P., and Eiserson, Leo: The Influence of Protein and Inorganic Phosphorus on Serum Calcium, J. Biol. Chem. **84**: 155 (Oct.) 1929.

Association News

ANNUAL CONGRESS ON MEDICAL EDUCATION, LICENSURE AND HOSPITALS

Palmer House Chicago February 17 21

Second Supplement to the Program Published Dec 14, 1929

MONDAY BANQUET

The banquet to be held on Monday evening, February 17, at 6 30, will be for the entire congress and will be given under the auspices of the Council on Medical Education and Hospitals and the Central Council for Nursing Education as joint hosts The speaker will be Dr Robert Maynard Hutchins, president of the University of Chicago Hon Ray Lyman Wilbur, Secretary of the Interior and chairman of the Council on Medical Education and Hospitals, is expected to preside It will be a formal banquet and ladies in attendance at the conference are most cordially invited

JOINT MEETING OF THE STATE HOSPITAL ASSOCIATIONS OF ILLINOIS, INDIANA AND WISCONSIN

The joint meeting of the State Hospital Associations of Illinois, Indiana and Wisconsin will be held at the Palmer House, February 20 and 21, two days immediately following the Congress on Medical Education, Licensure and Hospitals The tentative program is as follows

THURSDAY FORENOON, FEBRUARY 20

DONALD M MORRILL M D Presiding
Medical Director Blodgett Memorial Hospital and President Michigan Hospital Association Grand Rapids

Four Major Problems in Hospital Administration
Bert W Caldwell M D Executive Secretary American Hospital Association, Chicago

The Absorption of Special Charges
L C. Austin Superintendent Mount Sinai Hospital Milwaukee and Secretary Wisconsin State Hospital Association

Endowments for Schools of Nursing
Speaker will be announced later

The Proper Ratio of Personnel to Patients
Speaker will be announced later

THURSDAY AFTERNOON

J W MEYER Presiding
Manager Aurora Hospital and President, Hospital Association of the State of Illinois Aurora

The Superintendent s First Steps in Planning a New Hospital
Speaker will be announced later

The Coordination of Departments
Speaker will be announced later

The Cost of Illness
Speaker will be announced later

How the Social Worker Should Cooperate with the Other Department Heads
Edith Eichhoff A.B Assistant Professor of Social Service Indiana University Indianapolis

FRIDAY FORENOON, FEBRUARY 21

ALBERT G HAHN Presiding
Business Manager Protestant Deaconess Hospital and President, Indiana Hospital Association Evansville

Staff and Departmental Meetings
Speaker will be announced later

What a Hospital Trustee Should Know
Speaker will be announced later

Trustees' Meetings
Speaker will be announced later

The Relation of the Superintendent to the Board of Trustees
Speaker will be announced later

FRIDAY AFTERNOON, FEBRUARY 21

JOHN W COON M D Presiding
Medical Director River Pines Sanatorium and President Wisconsin Hospital Association Stevens Point

Public Relations
Speaker will be announced later

Emergency Work in the General Hospital
Speaker will be announced later

The Hospital Dietitian
Speaker will be announced later

Business meetings of the individual hospital associations are planned for Wednesday, February 19

THURSDAY EVENING BANQUET

A banquet will be held, Thursday evening, at 6 30, under the auspices of the joint hospital associations of Illinois, Indiana and Wisconsin Dr Christopher G Parnall, medical director of the Rochester General Hospital and president of the American Hospital Association, will preside

REDUCED RAILWAY FARES

All those attending the joint meeting of the state hospital associations are eligible to receive such reduced railway fares as may be secured for the Congress on Medical Education, Licensure and Hospitals On buying their tickets to Chicago all should *obtain certificate receipts* which, when countersigned, will entitle them to one-half fare for their return tickets

MEDICAL BROADCAST FOR THE WEEK

The American Medical Association Morning Health Talks and Evening Health Hints from Hygeia

The American Medical Association broadcasts daily at 10 o'clock Central Standard Time, with the exception of Friday, when the health message is delivered at 9 45, over Station WBBM (770 kilocycles, or 389 4 meters)

The program for the week of January 6-11 is as follows

January 6	The Safeguarding of School Equipment in Manual Training by Dr John M Dodson
January 7	The Ubiquitous Wash Cloth by Dr R. G Leland.
January 8	X Rays—A Two-Edged Sword by Mr H J Holmquest.
January 9	Overtired Children by Miss Mildred Whitcomb
January 10	Warning Signals of Fatigue by Mr Cecil Bean
January 11	Medicolegal Anecdotes by Mr T V McDavitt

Evening Health Hints from Hygeia, 8 o'Clock, Central Standard Time

January 6	The Conflict with Quackery
January 7	Off Duty
January 8	Professional Patchwork
January 9	Looking Backward.
January 10	Early Diagnosis and Happiness
January 11	Knowing Tuberculosis.

THE DETROIT SESSION

Scientific Exhibit Announcement of Exhibit by Section on Radiology

The Section on Radiology has appointed the following members as the Committee on Section Exhibit Ross Golden, M D, New York E R Witwer, M D, Detroit, and P M Hickey, M D, Ann Arbor, chairman

The committee again points out that one of the functions of the Section on Radiology is to cooperate in educational matters One of the ways in which this educational program can be fostered is by the members of the Section on Radiology arranging a well selected exhibit for the Detroit Session. The committee therefore invites applications for exhibits of investigative character dealing with the subject of radiology

The radiologic exhibit may be in the form of original films or reduced transparencies Prints, provided they are suitably mounted on cardboard, are also quite desirable. In case either of transparencies or of prints particular emphasis should be placed on the use of amply printed explanatory legends a third dimensional exhibit correlating the films is particularly impressive. As in the case of all exhibits in the American Medical Association, personal demonstration is required

The members of the specialty are asked to take an inventory of the materials that might illustrate phases of radiology, and communicate with the committee chairman Dr P M Hickey University Hospital Ann Arbor, Mich All applications must be made on the regular application form which is the one required by the A M A Committee on Scientific Exhibit A circular letter giving information concerning this exhibit together with the usual application blank, has been sent to all those who have registered in the section during the last three years Those who have not registered in this section but who are interested in such an exhibit may obtain a circular letter and application blank by sending the request to Dr Hickey Applications should be filed not later than March 1 with Dr Hickey

Medical News

(PHYSICIANS WILL CONFER A FAVOR BY SENDING FOR THIS DEPARTMENT ITEMS OF NEWS OF MORE OR LESS GENERAL INTEREST SUCH AS RELATE TO SOCIETY ACTIVITIES NEW HOSPITALS EDUCATION PUBLIC HEALTH ETC)

COLORADO

Personal —Dr Carl H Graf has been appointed health officer of Boulder ——Dr Basil G Carson, secretary of the Arapahoe County Medical Society, has been appointed health officer of Englewood to succeed the late Dr Arthur O Tiedt

Communicable Diseases in General Hospitals—In the last three years, the Colorado General Hospital, Denver, has treated in its wards practically all local types of communicable diseases without a single cross-infection says the committee on hospitals of the Colorado State Medical Society in its annual report The committee believes that it has been definitely demonstrated that communicable diseases can be cared for in general hospitals with no danger to other patients Physicians of the state should educate the public, therefore the report states, so that it will be possible to care for tuberculosis and communicable diseases in general hospitals

DISTRICT OF COLUMBIA

Tour of French Physicians —An official tour of three physicians, appointed by the French ministry of labor and health, began recently at Washington The visiting physicians are Drs André Bloch, J M Le Mee and Jean Dalsace, who have come to study surgical and medical methods used in the United States They will go on to Baltimore, Chicago, Detroit, Rochester, New York and Boston

FLORIDA

Yale Establishes Monkey Farm at Orange Park.—The Rockefeller Foundation has given $500,000 to Yale University New Haven, Conn, which will be used to establish a laboratory station on a 200 acre tract at Orange Park for the breeding and scientific study of anthropoid apes A special laboratory will be built in which will be made a detailed observation of the habits social relations, life history and psychobiologic development of the chimpanzee, the gorilla, the orangutan and the gibbon. It is thought the exhaustive studies of anthropoids will be of great importance in connection with the program of the Institute of Human Relations at Yale The studies will include problems in physiology, behavioral adaptivity, mental defects and diseases among the apes and it will be under the general supervision of Robert M Yerkes, Ph D., who has been at work at Yale for five years on comparative psychobiology There will be an advisory council including representatives of Yale and Edwin G Conklin, Ph D Princeton University Dr Milton J Greenman of the Wistar Institute Philadelphia Dr Theobald Smith of the Rockefeller Institute Clark Wissler Ph D, of the American Museum of Natural History New York Dr H Gideon Wells of the University of Chicago and John C Merriam Ph D president of the Carnegie Institution of Washington

ILLINOIS

Personal—Dr George Hoffman after about twelve years' service as physician at the prison at Chester has resigned effective January 1 to devote his time to private practice ——The home of Dr and Mrs Christian H Diehl Effingham is reported to have been destroyed by fire Dec 19 1929

Society News—Dr Joseph K Calvin Chicago gave an illustrated lecture on Nephritis in Children before the Livingston County Medical Society, Pontiac Dec 19 1929 ——At a meeting of the Winnebago County Medical Society Dec [illegible] 1929, at Rockford Dr Harry B Culver of Northwestern University Medical School Chicago spoke on Trauma as a Factor in Genito Urinary Diseases ' and Dr James G Carr, Jr of Northwestern University Medical School Diagnosis of Early Cardiac Failure ——Dr Carl E. Black Jacksonville was elected president of the Western Surgical Association for the ensuing year at the recent meeting in Del Monte, Calif

Chicago

Impostor K N Marx Convicted—Kurt N Marx 4336 Sheridan Road, Chicago was convicted before Judge Holmes Dec 10 1929 for violation of the medical practice act, and was sentenced to six months in the Bridewell The conviction was secured through the activities of the department of registration and education According to the report Marx examined a 15-year old girl at the request of her father who believed that Marx was a registered physician Marx called at the girl s home where, after making an examination he told the mother that her daughter had syphilis He then collected $40 from the father, claiming that he would send to Germany for medicines to be used in treating this disease Marx also examined the father and advised him that he had tuberculosis He examined an uncle of the girl from whom he collected money for treatment but which he returned after his arrest

Society News—Dr Fritz Wittels Vienna will lecture January 6, 8 and 10 at the Chicago Woman s Club under the auspices of the Illinois Society for Mental Hygiene and the Chicago Association for Child Study and parent education on Psychoanalysis and Other Contemporary Schools Freud s Idea on Sex and the Super-Ego and 'Comparison of the Primitive the Child and the Dream Mind ' The fee for the course is $2 50 ——The Chicago Dental Society will hold its annual congress at the Stevens Hotel January 13-15 A symposium on avitaminoses will be presented by Dr Simeon B Wolbach Shattuck professor of pathology and anatomy Harvard University Medical School Dr Edward H Hatton professor of pathology, Northwestern University Dental College and Milton T Hanke, Ph D, professor of pathology, University of Chicago Many other speakers will take part in this program Physicians are especially invited to attend the foregoing symposium

INDIANA

Thirty-Six Dead in Meningitis Epidemic—The outbreak of cerebrospinal meningitis at Indianapolis up to Dec 30, 1929 is reported to have caused thirty six deaths and there were a number of cases under treatment The type of this outbreak was said to be unusually virulent Extensive measures had been taken to prevent the infection from attacking other communities but a small outbreak was reported at Columbus, Ind

Society News—After the business meeting of the Tippecanoe County Medical Society, Dec 12, 1929 the members and their families spent the remainder of the evening at bridge and euchre The secretary Dr John C Burkle believes that county medical societies would benefit by more frequent social gatherings in which the families take part ——Dr John A MacDonald was elected president of the Indianapolis Medical Society at its meeting in Indianapolis Dec 4 1929 ——Dr Fred N Daugherty has been appointed health officer of Crawfordsville it is reported to succeed Dr Thomas Z Ball

IOWA

Society News—The Calhoun County Medical Society conducted a symposium Nov 21 1929 on An Obstetric Platform ' Dr Palmer Findley Omaha presided Dr Fred L Adair, of the University of Chicago Medical School and chairman of the joint committee on maternal welfare appointed by the American Medical Association gave an address on The General Practitioner and Obstetrics many Iowa physicians took part in the symposium ——The Fayette County Medical Society held an all day meeting Nov 26 1929 beginning with a surgical clinic at the Mercy Hospital in the forenoon Dr George L. Apfelbach Chicago conducted diagnostic clinics at the same hospital in the afternoon In the evening Dr Apfelbach presented a paper on 'Surgery in Diabetic Gangrene' illustrated ——The Polk County Medical Society Des Moines at the November 1929 meeting was addressed by Drs A G Fleischman and L E Kelley on bilateral polycystic kidney after which a three reel motion picture of infections of the hand was shown ——The Woodbury County Medical Society held a noonday dinner meeting Nov 22, 1929 in Sioux City the speakers being the mayor Mr T B Huff the superintendent of schools Mr M G Clark the city attorney Mr H C Shull and the new city physician Dr E B Godfrey At the scientific session

HYDROSULPHOSOL IN THE TREATMENT OF BURNS AND INJURIES OF THE CORNEA

Major Y. K. C. Pandit *

Burns and injuries of the cornea present a major problem to an ophthalmic surgeon. Firstly he has to answer that eternal query of the patient 'Doctor, will my eye be saved ?' Secondly, his thoughts run on the various lines of therapy he has adopted in such cases and to consider one that would be most suitable to the particular case. Orthodox methods of therapy used so far have presented many difficulties. The nature of the chemical has to be known in order to neutralise it with its antidote. This involves a vast knowledge of chemistry for an ophthalmic surgeon. Even this therapy is only partially effective as it merely neutralises the excess of the chemical, and prevents further damage, but has neither any action on the damaged tissue nor does it help its repair. The complications which follow are hardly minimised. The obvious results in the past experience have been, that the hospitalisation is a prolonged one, the end results have never been entirely satisfactory, and very often, on recovery, the patient leaves the hospital either with a dense leucoma, or a diminished vision, or with a large symblepheron, complications, which are a headache for plastic surgery at a later date.

My attention was first drawn to hydrosulphosol therapy last year by Dr. Hedwig Kuhn in a personal communication and the reprint sent with it contains an interesting paragraph which I quote below.

"When a therapy is so outstanding as to leave no doubt of its efficacy, as evidenced by repeated application which elicits prompt and favourable response in case after case, then that therapy cannot be ignored."

This therapy renders the age old practice of neutralising the chemical obsolete and aims at neutralising the effects of the substance. The nature of the chemical is immaterial to the line of treatment to be adopted and the therapy fulfills the important requisitions in the treatment of burns viz., a) exclusion of air ; b) analgesic, antiseptic and non-toxic ; c) leaves a dry, sterile and flexible scar ; and d) stimulates epithelial proliferation.

REVIEW OF LITERATURE

The main theme revolves round sulphur metabolism. According to Klauder and Brown,[7] skin is the depot for sulphur, and demands are made on that depot for any defence against infection or intoxication. Burns deplete the store of sulphur by damage to the tissues. The mechanism of tissue respiration and repair is thrown out of gear. The supply to the organ concerned with detoxication is reduced and restricted. Croft and Peters[3] found that methionine, the sulphur containing amino-acid, prevents loss of nitrogen in urine in cases of severe burns, and thus protects against the loss of protein.

---

* Department of Ophthalmology, G. T. Hospital, Bombay.

Glutathione is composed of two amino-acids—cysteine and glutamic acid bound by dipeptide linkage. It occurs in animal tissue and its concentration runs parallel to the metabolic activity of the tissue. With cysteine the cell proliferation is accelerated, and the glutamic acid helps in the selective building up of the protein molecule. Localio *et al*[9]. observe that "the processes of tissue destruction and repair are chemical in nature." Working on the subject of wound healing in animals depleted of proteins, they observed the effects of dl-methionine selected because of its sulphydryl radical. The–SH radical is important for its enzyme action, the–SH containing enzymes, acting as catalysts in the metabolic cycle. Should these be blocked there is inhibition of the enzyme activity, but should they be in excess the glutathione retards this inhibition and accelerates the enzyme action. Localio *et al*[9]. are of opinion that–SH enzymes play an important role during states of repair.

Reimann[13] as far back as 1930 reported that sulphydryl compounds stimulate the proliferation of epithelium. He used thiocresol in his work. Brunsting[2] used cysteine, prepared from hair.

The work on Hydrosulphosol was pioneered by Dr. R. R. Mellon[12] of Pittsburgh and the first results of the study were published by Mc Broom.[11] Mellon's[12] tissue culture experiments with hydrosulphosol show "not only does the normal growth occur, but in dilutions of 1 : 500 to 1 : 1000 the important function of the chick heart embryo fibroblasts undergoes marked stimulation. This function is a proteolytic one, whose differentiating and therefore, healing connotations align themselves with the clinical expressions in this connection. This functioning in high dilutions, suggests that the effect is an enzyme one. In fact, the–SH linkages are well known to function as co-enzymes in certain respiratory systems, implementing cell nutrition."

The pH of hydrosulphosol solution is 10 and on dilution it reaches a level favourable for function of an injured tissue. With a dilution of 1 : 40 the pH is 8.2 and with a dilution of 1 : 20 the pH is 8.5.

Pierce as quoted by Cruthirds[5] observed the output of sulphur in the urine in terms of SO_3 after application of hydrosulphosol in maximum quantities. The output during the first 24 hours was 9.3 gms and during the next 24 hours 7.92 gms. The normal output being 1.5 to 3 gms per day.

As regards the role of sulphur in the eye, Mackay[10] and co-workers have shown that half the total ash of the lens consists of sulphates derived from glutathione, cysteine and other compounds containing sulphur. In the opinion of Reiss and Jess[14] glutathione plays an important role in maintaining the function of the lens. Any alteration in the capsular permeability leads to imbalance in the interchange of the nutritional material and the waste products, with the result that the toxic compounds increase and glutathione is reduced. In senile cataract sulphydryl disappears.

Cruthirds[5] reports 500 cases of burns involving eyes and treated with hydrosulphosol. His findings on this therapy are: (i) the after-scarring is considerably reduced; (ii) scarring is less than normally expected; and (iii) there is absence of symblepheron. In his opinion the results are due to therapy which is capable of stimulatng cell activity and also produces healing in a short space of time. Cruthirds[4] considers this local therapy as one which fulfils many requisites and is superior to any with which we are so far familiar. It offers many advantages in that it stimulates cell proliferation, prevents or abates infections, is non-toxic, and relieves pain.

Kuhn[8] reports on 300 cases of major chemical and thermal eye burns treated with hydrosulphosol with good results and considers the results vastly superior to those observed during the previous years when approved methods were used. From Kuhn's results one can again emphasize the following points: faster healing with less impairment of vision as a permanent disability, and the occasions when surgical interference was necessary or the complications like contractures ensued, were few. The simplicity of the technique is in itself attractive.

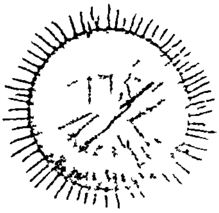
MODES OF APPLICATION

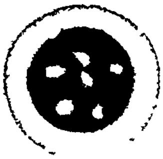
The therapy can be used as hydrosulphosol eye drops with a dilution of 1 : 40 in warm triple distilled water at intervals of 30 minutes or longer depending on the severity of the case; or 1 : 20 as compresses. It can also be used as a hydrosulphosol concentrate in castor oil in a dilution of 1 : 20. This has a tendency to settle but can easily be put into solution by shaking the bottle.

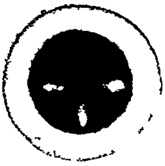
The eye is first washed copiously with water in acute cases and pantocaine anæsthesia instilled. Homatropine in mild cases and atropine in severe cases is used for mydriasis. The conjunctival sac is filled with the solution and the eye bandaged. The treatment is repeated after 24 hours, checking the areas of damage by staining.

We used the concentrate in castor oil and observed the results after every eight hours. The drug is not available in the local market. I was fortunate to obtain a small quantity from Dr. Dastoor of the Tata Mills, Tata Sons Ltd, when I expressed my difficulty about the first case and my desire to study its efficacy.

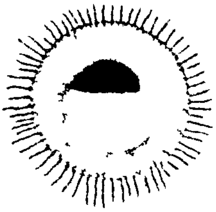
CASE 1

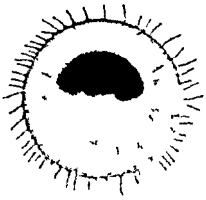

6-1-50

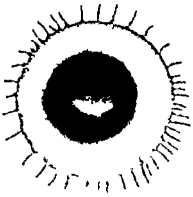

8 1 50

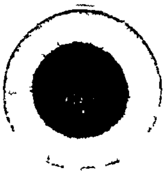

10-1 50

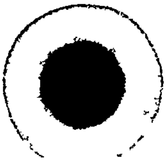
CASE 2


28 3 50

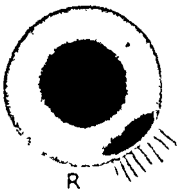

28 3 50
AFTER 8 HOURS

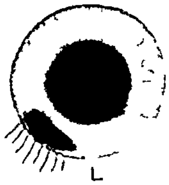

29 3 50
24 HOURS

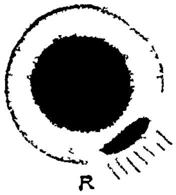

30 3 50
AFTER 48 HOURS

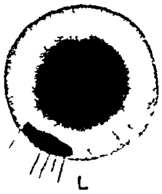

1-4 50

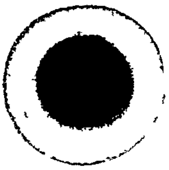
CASE 3


10 4-50



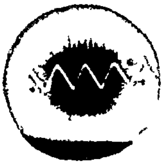

8 HOURS LATER

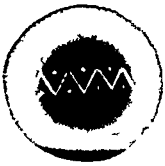

8 HOURS LATER

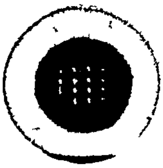

11 4-50
24 HOURS LATER

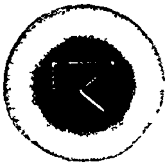
NOT STAINING

CASE 4


25-6-50

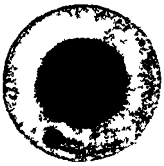

26 6 50


29 6 50


30 6 50

NOT STAINING

CASE 5



CASE RECORDS

Most of these cases were injuries to the cornea and as the quantity of the drug at my disposal was small I used it only in severe cases. The appearance before the commencement of the treatment and the follow up from time to time are given as coloured pictures of which sketches were made at the time of treatment.

Case 1. Mr. D. aged 55 had developed a conjunctivitis which subsequently developed into a keratitis and ulcer of the cornea, following some local treatment at home (the nature of the chemical instilled into the conjunctiva being unknown). He was admitted to the hospital on 14-12-49. Local applications, penicillin, and sulphonamides gave no relief. The cornea showed marked vascularity and ulceration. The pain, photophobia, lachrymation and neuralgia were intense and were not relieved by salicylates. Insomnia was causing great strain on the patient. On 6-1-50 hydrosulphosol therapy was commenced as a concentrate in castor oil and was given as 8 hourly instillations in the conjunctival sac. On 8-1-50 the cornea only showed a faint staining as streaks and spots, the pain was relieved, the photophobia, however, persisted. By 10-1-50 the cornea was showing only thin lines of staining at three places, the vascularity had considerably diminished and by 11-1-50 the lustre of the cornea was practically normal, the anterior chamber was deep, and the iris pattern was visible at the periphery. On 13-1-50 the eye was quiet and had practically returned to normal. Hydrosulphosol was omitted on the 17th. The end result was a triangular thin scar with its base on the outer side and partially covering the pupil. The vision was 2/60. The patient was discharged on 26-1-50.

Case 2. G. H. S. a postman aged 35 had been out of Bombay for some game shooting, and his right eye sustained burns on 24-3-50 from the smoke from the rifle after the shot was fired. He was admitted to the hospital on the night of the 27th. The bulbar and palpebral conjunctiva were markedly chemosed. The cornea showed a large area of burn, uneven and slightly raised which almost covered a little more than a third of the corneal surface and was located centrally. The Descemets membrane showed some striae of induration above the ulcer. The vessels of the conjunctiva above the limbus were of a corkscrew pattern, splitting into small parallel capillaries at the limbus and running on the cornea up to a distance of 2 mm. all round. The limbus in the upper part showed slight elevation. Scrapings from the ulcer showed pus cells but no organisms were detected. Hydrosulphosol in castor oil was instilled as the therapy of choice. The cornea was stained with fluorescein before each instillation. By 10 p.m. on the 28-3-50 the area of staining was considerably reduced. Chemosis persisted but there was no pain. The ulcerated area and the chemosis were much less next morning and by evening of the same day the descematitis showed signs of abatement. On 30-3-50 the vessels on the cornea could not be seen, the conjunctival vessels were comparatively few and the cornea had slight haziness. On 31-3-50 the conjunctival vessels had cleared and the ulcer was replaced by a small thin opacity covering about two thirds of the pupillary area. The patient was discharged on 3-4-50 and at the time he left the hospital the vision was 6/18.

Case 3. R. P. D. aged 20 had both his eyes injured by molten lead and was admitted to the hospital on 10-4-50 with burns of the first degree on the left upper lid, nose and naso-orbital groove. Both corneas were burnt along the margins and showed deep staining ulcers. There was slight vascularity in the region of the burns at the limbus. His vision on admission was 6/60 each eye and improved to 6/6 each eye with -3.00 Dsph. Hydrosulphosol in castor oil was instilled twice a day.

By 12-4-50 the cornæ were normal, no scar could be seen and the patient was discharged on 14-4-50. He was prescribed spectacles on 26-4-50 and the aided vision was 6/6, each eye.

Case 4. Mrs. M. M. aged 35 was admitted to the hospital on the afternoon of 5-6-50 having an injury to her right eye from fireworks. The injury occurred three hours before admission to the hospital. In addition to small contused wounds on the lids she had hæmorrhage into the anterior chamber, the cornea showed zig-zag patterns of white lines spreading horizontally across in a band shaped manner. The areas in between the lines showed deep staining with fluorescein. No vascular patterns were visible. Atropine was instilled and hydrosulphosol therapy was commenced immediately. By 28-6-50 the ulceration was healed but the white lines on the cornea were still visible. Vision was only perception of light. Hydrosulphosol was omitted on 30-6-50 as by this time the cornea was practically normal and hyphæma had disappeared. She was discharged on 3-7-50 with a fine linear scar on the cornea and the vision was 6/36 with the atropinised pupil.

Case 5. V. B. a girl aged 10 was accidentally injured across the right eye and nose with a stick while playing. The right cornea showed a large ulcer covering almost three fourths of the cornea. She presented herself at the hospital on 20-1-50 a few hours after injury. The eye was cleaned and atropine instilled and the hydrosulphosol therapy commenced. On the 23rd the eye was quiet and the area of staining on the cornea was restricted to a small patch near the margin. By 25-1-50 the eye was normal. This patient was treated at the outpatient department.

COMMENTS

Past experience shows that such cases treated along orthodox lines take a long time at the hospital before they are fit to be discharged and the end results are far from satisfactory. The cases treated with hydrosulphosol were considered cured or had maximum benefit in from 3 to 21 days in my small series of cases. Pain was relieved quickly, the scars were soft and the ultimate vision was satisfactory. There were no complications in the present series.

I have to thank Dr. M. V. Modi, Superintendent, of the G. T. Hospital for his kind permission to publish these cases. My thanks are also due to: Dr. F. P. Dastoor of Tata Sons Ltd. for the supply of Hydrosulphosol and the loan of literature, my clinical asst. Dr. M. C. Athawle, Dr. A. H. Nakhooda M.R.C.P., for help rendered in the preparation of this paper, and Mr. Hargopal of the Indian Art Studio for the paintings attached to this paper.

REFERENCES

1. Bellows, J. G.: Cataract and Anomalies of the Lens. pg. 212, St Louis, Mosby & Co., 1944.
2. Brunsting, L. A., and Simonsen, D. G.: Cutaneous Ulcers treated by the Sulphydryl containing Amino-acid cysteine, J.A.M.A. **101**: 1937-1940, 1933.
3. Croft, P. B., and Peters, R. A.: Nitrogen Loss after Thermal Burns. Effects of adding protein and methionine to diets of rats, Lancet **1**: 266-271, 1945.
4. Cruthirds, A. F.: Burns of the Ear, Nose, Mouth and adjacent tissues, Laryngoscope **53**: 478-494, 1943.
5. Cruthirds, A. E.: Importance of Sulphydryl in the treatment of Corneal and X-ray burns, Am. J. Surg. **72**: 500-509, 1946.

6. Hoffman, J. M.: Burns and Scalds, their Etiology and Prognosis, Am. J. Surg. **56**: 463-468, 1942.
7. Klauder, J. V., and Brown H.: Certain phases of Sulphur Metabolism of the Skin, Arch. Dermat. and Syph. **34**: 568-581, 1936.
8. Kuhn Hedwig, S.: The use of Hydrosulphosol (sulphydryl) in the treatment of chemical and/or thermal burns of the eyes, Indust. Med. **17**: 347-350, 1948.
9. Localio, S. A., Morgan, M. E., and Hinton, J. W.: The biological chemistry of wound healing; the effects of dl methionine on the healing of wounds in protein depleted animals, Surg. Gynec. and Obst. **86**: 528-590, 1948.
10. Mackay, G., Stewart, C. P., and Robertson, J. D.: A note on the inorganic constituents of normal and cataractous human crystalline lens, Brit. J. Ophth. **16**: 193-201, 1932.
11. McBroom, J.: The use of Sulphydryl Solution in Burns caused by Ultraviolet Radiation, M. Rec. **152**: 299-300, 1940.
12. Mellon, R. R.: A new Sulphydryl solution for the treatment of Burns, Indust. Med. **11**: 14-18, 1942.
13. Reiman, S. P.: Use and reasons for the use of Thiocresol to stimulate Wound Healing, J.A.M.A. **94**: 1369-1371, 1930.
14. Reiss, W., and Jess, A.: as quoted by Cruthirds.
15. Salle, A.J., and Korzenovsky, M.: Nature of hydrosulphosol and its toxicity on living embryonic tissue, Proc. Soc. Exper. Biol. and Med. **49**: 212-215, 1942.

GIARDIASIS IN CHILDREN

G. Coelho *

HISTORY

Giardia were described for the first time by Leeuwenhœck[18] in 1675 who saw them through his primitive microscope in his own stools. They were then forgotten, to be discovered again by Lambl in 1859, after whom they bear the name Lamblia. Lambl thought that Giardia belonged to the genus *cercomonas.* A detailed study was published by Grassi [11] in 1877. He first named the flagellate *Dimorphus muris* but changed the name later to *Megastoma entericum.* He demonstrated that the habitat of this parasite was the upper intestine, to the mucous membrane of which it attached itself by means of a sort a of sucking disc. He also reported that although the parasites were found in individuals who did not complain of any symptoms, yet sometimes they caused diarrhœa.

PATHOGENICITY

Giardia is found among many vertebrate hosts, mammals, reptiles, amphibians, birds and fish. In the human being it is found in the intestinal tract, from the duodenum to the caecum, in decreasing numbers Whether the giardia is pathogenic or is a harmless parasite never causing any symptoms, has been discussed for years by various writers. Nothnagel [26] (1881), von Jaksch (1888), and Joachim [15] (1909) considered it harmless. The opinion of Grassi [11] that it may cause diarrhœa was supported by Schewiakoff (1888) and Perroncito [29] (1902). Further studies led to the conclusion that giardiasis does produce symptoms. Lyon and Swalm[19] after a study of 3200 cases thought that giardia may be a contributory factor in diseases which involve the biliary tract, duodenum and jejunum. "Of the protozoan flagellates that inhabit the bowel of man, *giardia intestinalis* has the best claim to be regarded as pathogenic," writes Manson—Bahr [23]. Bhattacharjee[2] says that "Giardiasis is a definite disease," so also Rissman [31] and Katsampes [16] *et al.* Das Gupta *et al.*[8] reported fulminating cases resembling Asiatic cholera. From our experience in children, we are inclined to the opinion that this flagellate is pathogenic.

DISTRIBUTION

Giardiasis is widespread. In 1916-17, of the 6000 admissions to the Mayo Clinic, 6.6 per cent had giardiasis. Of 89 children examined by Maxcy[22] 14 were infested with the flagellate. Stils [32] said it was by no means uncommon in the U. S. A. and Faust [9] found it a relatively common infection of childhood. In Great Britain, Mathews and Smith [22] examined 548 children in the Liverpool Royal Infirmary and found 14 per cent infected. MacNutt [20] reported that 48.8 per cent of the inmates of a child institution and 23.9 per cent of the children that attended the Infirmary, harboured giardia. In Budapest, Veghelji [34] examined 1391 children between 2 and 17 years and found that 155 of them were infected. In France, Labbe [17] found that giardiasis in adults starts in childhood. Chantriot [4] found it very common in Beyruth. In Poland, Rissman [31] reported it to be as frequent as bacillary dysentery. It was also a cause of diarrhœa in the armed forces. In India, Napier [25] found 6.27 per cent of 20,000 stools examined between 1935 and 1938 positive for giardia. Das Gupta, Banerjee and Sen Gupta [8] reported that of 1000 stools examined at the Khulna District Board Laboratory between 1936 and 1943, 7.9 per cent were positive for giardia. They also remarked that the incidence of giardiasis in that district was rising in the last eight years, being ten times more in 1943 than in 1936. They have also observed a periodic exacerbation every fourth year. Chopra *et al.* [6] reported that at the Carmichæl Hospital for Tropical Diseases, Calcutta, giardia were found in the following percentage of stools examined: 5.8 per cent in 1934, 6.8 per cent in 1936, 4.7 per cent in 1937 and 7.6 per cent in 1938. In a series of 200 consecutive patients admitted to the Children's Hospital at Calcutta, Chatterjee [5] found 10.5 per cent had giardia. In Bombay, at the Byramjee Jeejeebhoy Hospital for Children, of 1577 stools and rectal swabs examined 164 (10 per cent) were positive for giardia. In another series of 131 stools and 224 rectal swabs 12 and 10 respectively were positive. At my office 1478 stools and 1271 rectal swabs of children seeking advice for acute or chronic diarrhœa were examined microscopically. Of these 197 (7.1 per cent) were positive. In this series the percentage of positive findings in the stools was 10 per cent but in the rectal swabs only 3.3 per cent. (Table 1).

---

* Byramjee Jeejeebhoy Hospital for Children, Bombay.

TABLE I. *Stool and Rectal Swab Examinations.*

	Stools	Rectal Swab
Total	1478	1271
Positive	154	43
Veg. Forms	30	33
Cysts	105	10
Veg. & Cysts	19	..

HABITAT IN MAN

The habitat of the flagellate is the small intestine, particularly the duodenum. It attaches itself to the wall by means of a concave peristome. The flagellate has also been recovered from the gall-bladder, at the time of operation. It has also been found in the B fraction of duodenal aspirate. The gall-bladder acts as a reservoir where it multiplies and grows. Multiplication takes place by binary fission in the long axis. A very large number of flagellates are found in the small intestine. In rabbits, Jassinowski [14] found a million flagellates per square centimetre of the gut. Encystation takes place in the large intestine. By their constant movement they set up an inflammation of the wall. Both the vegetative forms and the cysts are passed out intermittently and in uncertain numbers. Porter [30] enumerated the number of cysts passed in the stools per day. According to her they varied from 10 millions when the bulk of the stools was about 50 c.c. to 14,440 millions when the stool volume was 950 c.c. per day. The interval between successive maxima and minima excretion in the same patient being about 14 days.

In the vegetative stage the giardia is pearshaped, about 14 microns in length and 8 microns in breadth. It has two symetrical divisions. Each division has a nucleus and four free flagellæ. No foreign corpuscles or products of metabolism can be seen in the body. Nourishment probably takes place by osmosis. When seen in a specimen of a fresh stool, its activity as it flits across the field is remarkable and once seen is not forgotten. The cyst is smaller in size, has four nuclei and a network in the body. It is best seen after staining with iodine.

AGE INCIDENCE

In certain animals the young of the species show a higher infestation than the older animals. This is also true in human beings. In the same group of population the percentage of adults showing giardia cysts is one-third to one-fifth of that in children. This may be due to a change in the bacterial flora of the intestine. The relative frequency of this infection in early childhood has been noted by many observers. The maximum incidence is below the age of five years. The infection may be acquired quite early in life. Mac Nutt [20] found this infection in 6 children below one year of age of whom one was only three weeks old and the other three months old. In our series the youngest child was a month old; and the rest were as per table. (Table 2).

TABLE 2. *Age Groups.*

Months.	Nos.
0— 3	2
4— 6	6
7— 12	25
13— 24	30
25— 60	91
61—120	35
121+	

MATERIAL

It is well-known that even with giardia in the stools, there may be no symptoms. But it may be found in the stools of those children who are brought with the complaint of either acute or chronic or recurrent diarrhœa. Of 152 children whose history is studied and in whose stools and rectal swabs giardia were found, there were no symptoms in 41 children. Seventy-two were brought with a history of acute diarrhœa, 29 with a history of recurrent diarrhœa, in some extending as long as three years, and 16 with a history of continuous subacute diarrhœa for about a month. The flagellates may be the only abnormal finding in the stool or there may be more suggesting other infections. Vegetative forms were found in 63 children, cystic forms in 115, and both were found in 19 children. Ten children had, in addition, infection with *E. histolytica*, nineteen had macrophages in the stools, forty-two had pus cells, and twenty ascariasis infection.

TABLE 3. *Diarrhœa History*

Total No.	No complaints	Diarrhœa		
		Acute	Recurrent	Continuous Subacute
158	41	72	29	16

SYMPTOMATOLOGY

1. *Stools.* In the acute phase there is a great urgency, so much so that the clothes often get soiled. The stools are large, passed with force and flatulence. In 41 children the stools were watery and in 31 soft, porridgy and contained mucus. They spread over a large area, and when passed squatting on the floor are liable to spurt on the feet and lower part of the legs. They are usually yellow in colour, have the appearance of a *dhal* curry which is badly mixed. When allowed to stand in the test-tube the porridgy matter settles at the bottom with a fairly clear yellowish fluid on top. Usually they smell badly, but all are not offensive. Sometimes they contain blood and mucus and the attack simulates one of bacillary dysentery. They may be five or six a day, or as many as thirty to forty a day. The frequency is quickly controlled by treatment; even without it the stools decrease on their own. They are usually not post-prandial. They are acid in reaction. There may be excoriation of the buttocks around the anal area. In Veghelji's[34] study free fatty acids comprised two-thirds of the excreted fat and the acidity reached an extreme pH of 4.0. It seems that the nature of the intestinal contents determines the excessive peristalsis. The extreme acidity and the collection of excessive fat, other nutritive material, water and secretions is responsible for the diarrhœa. In the subacute and chronic stage the stools may be large, whitish, offensive and resemble the stools in steatorrhœa.

Those children whose stools contained the vegetative along with the cystic forms came with a history of acute diarrhœa, namely increased frequency, urgency, flatulence, watery, acid stools. The children whose stools contained only the cystic forms came with a story of either prolonged subdued diarrhœa which had not responded to sulfa drugs etc. or one that had recurred over and over again. The stools were three or four a day with plenty of mucus. When there is any other infection there may be pus cells, red blood cells, macrophages and even *E. histolytica.*

2. *Abdominal Symptoms.* Distension of the abdomen is usually present. The feel may be only doughy between the acute attacks. In the acute phase the distension may be marked. Pain is present, though in my experience it is not a presenting symptom even in older children. Twenty two children complained of abdominal pain.

3. *Fever.* If it is not a mixed infection, fever is absent. There are no signs of toxæmia.

4. *Dehydration.* This will depend on the frequency and consistency of the stools. Frequent, watery stools are definitely followed by dehydration and consequent effects of dehydration.

5. *Anæmia and Malnutrition.* Children with such chronic infections of over six months duration naturally are undernourished and anæmic. The blood was examined in 44 children and the findings were as per Table 4.

TABLE 4. *Blood Examination*

R. B. C.	No.	Hgb %	No.
Between		0—30	1
2—3 million	3	51—60	6
3—4 ,,	25	61—70	12
4—5 ,,	16	71—80	17
		81—90	8

The percentage of eosinophils varied from 1 to 24; in seven children the percentage was more than 10. Chatterjee[5] reported œdema of the feet, but we have not found this degree of malnutrition in pure infection of giardia where dietary intake was adequate. Veghelji [33] studying these effects of giardiasis discounted the probability of the flagellate eating the red blood cells as the cause of the anæmia, because red blood cells have not been seen in the body of the flagellate. He is inclined to think that the anæmia may be due to the harmful effect on a hæmopoietic substance, or to an imperfect absorption of nutrition because the flagellate lines the wall of the intestine.

6. *Poor absorption.* Veghelji [34] also noted that though the fermentative activity and splitting of fat was normal, the stools contained excess of fat because of poor absorption. Katsampes *et al.*[16] studied vitamin A

absorption in 15 children suffering from giardiasis and found that they did not absorb the vitamin as well as normal children did the curves being relatively flat and there being a delay in reaching the maximum value. The fat content of the stools decreases, the absorption of vitamin A improves and the excretion of urinary pigments increases soon after treatment with atebrin or quinacrine hydrochloride. The concentration of urinary pigments is far below normal. Malnutrition, naturally, does result from the improper absorption of food. The majority of those suffering from chronic diarrhœa are undernourished.

7. *Chronicity.* An important feature of this infection is its chronicity and its tendency to recurrent attacks of acute diarrhœa. Giardiasis ranks high as a cause of recurrent diarrhœa in children. Twenty-nine out of 142 had recurrent attacks of diarrhœa and 19 chronic diarrhœa. Patel [28] found 62 out of 221 cases of chronic diarrhœa had giardia infection. One should not forget that the stools may sometimes contain blood, either in a good quantity or streaking a stool that is whitish, pasty and shining with mucus. In between the acute phases the stools may be three to four a day, whitish, of the consistency of a custard, covered with mucus and offensive. The stools may simulate those found in steatorrhœa. The child complains of pain in the abdomen, vague all the time, or at the time of the stool.

DIAGNOSIS

A history of very frequent stools with urgency, without fever or vomiting, particularly recurrent attacks in a child who has not put on weight for some time should always arouse suspicion of this infection. The diagnosis is easily confirmed by a microscopic examination of the stool and the finding of the cysts. However an examination of a stool is not enough, if it is negative. Repeated examination on different days is desirable. Seeing the wide disparity between the percentage of positive findings in the stools and rectal swabs one is inclined to prefer a stool examination. Coelho [7] found the rectal swab valuable but his cases were mostly acute.

TREATMEN

The treatment is simple. To be effective it must be persevered with for at least three months. In 1937, Brumpt[3] reported cures in 80 per cent of his animals with the administration of 1 per cent solution of basic acridine dye by mouth. In the same year Galli-Valerio [10] used a derivative of acridine, commercially called 'atebrin' and had striking results in curing a patient infected by giardia. Subsequently, Bacigalupo[1] in 1938 and Dr. Muro [24] in 1939 reported successes with this drug. Now it is the drug of choice. We observe the following routine :—

Mepacrine. Mepacrine for seven days. The dose of mepacrine is ⅓ tablet thrice a day in children up to 2 years of age, ½ tablet thrice a day in those up to five years, ¾ tablet thrice a day up to 8 years and 1 tablet thrice a day above that age. Each tablet of mepacrine contains 0.1 G of the drug.

Acetarsol (Stovarsol.) The dose of stovarsol is ¼ gr. once a day up to 2 years of age, twice a day up to 5 years, thrice a day up to 8 years, and four times a day after that. The course is for three weeks.

In addition dilute hydrochloric acid with glycerine pepsin before food, and iron, liver and vitamin B complex are prescribed orally after food. During the acute phase a bismuth mixture is given to control the frequency, though I am inclined to think more and more that this can be omitted. The diet in the acute stage is fresh curds obtained by breaking milk with sour-lime juice, ripe bananas, plenty of fluids. Dehydration should be prevented by maintaining adequate fluid intake, orally or if need be, parenterally.

The response to mepacrine is very quick. In 24 hours the number of stools may come down in frequency from 30 to 5 per day. The child's general condition improves, and he becomes more restful. By the end of the course of treatment both cystic and the vegetative forms disappear from the stools. I repeat mepacrine and stovarsol in the same order for three months and maintain the dilute hydrochloric acid, vitamin B complex and iron for the duration of the course.

PREVENTION

Once the infection is acquired its duration has not been determined. So far no intermediate host has been described. It seems that the infection is transmitted directly by contaminated fingers. The cysts can remain alive outside the human host for only a few hours. It is common to find more than one member of a family suffering from this infection. In our country, with our unhygienic toilet habits, it is easy to transmit the infection from person to person. Hence it is desirable that the stools of other members of the household should be repeatedly examined, particularly if there is a history of diarrhœa at the time when the stools are loose. One cannot write too strongly on the need of educating our people in hygienic toilet habits; this should be a matter of top priority. Dobbel wrote "it has not yet been demonstrated in any particular instance that an individual once infected with giardia has subsequently been ridded of the parasite." That was in 1920. But to-day with the use of mepacrine and stovarsol the outlook is better and the infection can be conquered.

REFERENCES.

1. Bacigalupo—cited by (12).
2. Bhattacharjee, I: Giardiasis, Ind. Med. Gaz. **78** : 91-92, 1943.

3. Brumpt, Lucien, Traitement experimental de la lambliase, Comp. rend. Soc. de Biol. **124** : 1040-1042, 1937—
4. Chantriot, P. : L'amibiase et la lambliase du Nourrisson, La Presse Medicale No. 82, 1589, 1930.
5. Chatterjee, R. : Giardiasis in Children, J. Ped. **6** : 158, 1939.
6. Chopra, R.N., Das Gupta, B.M., Sen, B., and Ahmed, Z. : Infection with Giardia Lamblia, Ind. Med. Gaz. **74** : 458-460, 1939.
7. Coelho, E. : Rectal Swab in the Investigation of Diarrhœas in Children, Ind. Jour. Med. Sci. **3** : 266-271, 1949.
8. Das Gupta, N. C., Banerjee, P. K., Sen Gupta, S. B. ; Fulminating types of Giardiasis Simulating Asiatic Cholera and Acute Bacillary Dysentery, J. Ind. Med. Assoc. **13**: 317-318, 1944.
9. Faust, E. C. : The Chemotherapy of Intestinal Parasite, J. A. M. A. **117** : 1331-1335, 1941.
10. Galli-Valerio, B.—cited by Hartman and Kyser (12).
11. Grassi, B.—cited by Maxcy.
12. Hartman, H. R., and Kyser, F. A. : Giardiasis and its Treatment, J.A.M.A. **116** : 2835-2839, 1941.
13. Hartman, H. R., and Kyser, F.A. :. Infection of the Gall-Bladder by Giardia Lamblia, J.A.M.A. **118** : 608-609, 1942.
14. Jassinowski, M.A.—cited by Veghelji.
15. Joachim, G. cited by Veghelji.
16. Katsampes, C. P. McCoor, A.B., Phillips, W.A. : Vitamin A absorption Test in cases of Giardiasis, Am. Jl. Dis. Ch. **67** : 189-193, 1947.
17. Labbe' : L'infestation par la lamblia chez l'enfant, La Press Medicale No. 82, P. 1589, 1935.
18. Leeuwenhœck—cited by Hartman and Kyser (12).
19. Lyon, B.B.V., Swahm, W.A. : Giardiasis, A.J. Med. Sc. **170** : 348-364, 1935.
20. MacNutt—cited by Maxcy, K. F.
21. Mathews and Smith, cited by Maxcy, K. F.
22. Maxcy, K. F. : Giardia Intestinalis, Bull. Johns Hopkins Hos. **32** : 166-170, 1925.
23. Manson-Bahr. : Tropical Diseases, pp. 258, London, Cassel & Co., Ltd.
24. De Muro, P.—cited by Hartman, H. R. et al (12).
25. Napier, Everard L. : The Principles and Practice of Tropical Medicine, pp. 452, Calcutta, Thacker, Spink & Co. (1933) Ltd.
26. Nothnagel, H.—cited by Veghelji.
27. Nutter, P. B., Rodaniche, E.C., and Palmer, D.L. : Giardia Lamblia Infection in Man, J.A.M.A. **116** : 1631-1632, 1941.
28. Patel, B. D.—Personal communication.
29. Perroncito—cited by Veghelji.
30. Porter, A. : An Enumerative Study of the Cysts of Giardia (Lamblia) Intestinalis in Human Dysenteric Foeces, Lancet **1** : 1166-1169, 1916.
31. Rissmann, S.S. : Lambliasis Intestinalis in Poland, Abs. J.A.M.A. **124** : 67, 1944.
32. Stills—cited by Maxcy, K. F.
33. Veghelji, P. : Giardiasis, Am. J. Dis. Ch. **56**: 1231-1241, 1938.
34. Veghelji, P. : Giardiasis, Am. J. Dis. Ch. **59**: 793-804, 1941.

URETERAL IMPLANTATION IN THE PELVIC COLON.

Two Case Reports

V. B. Davalbhakta *

A Vesico-vaginal fistula is always very difficult to repair. Failures in operation are very common. Hence it is thought worthwhile to report these two successful attempts to divert the urine into the colon and so relieve the patient of distressing dribbling.

Case I.

A 25-year old female was admitted on the 12th of May 1950 with a diagnosis of Vesico-vaginal fistula.

History in brief :—She was a primipara, who about 1½ months ago had a forceps delivery at Chahardi on the 3rd day of labour. Probably the head was fixed in the vaginal vault for a long time and during the application of forceps the anterior vaginal vault together with the base of the bladder must have been torn. For one month or so, she had been treated at the medical dispensary at Chopda from where she was directed to Jalgaon.

Physical signs :—The patient looked anxious, worried and anæmic. She was unable to walk, as a result of pelvic cellulitis and mild phlebitis.

Vaginal examination:—No anterior vaginal wall could be felt, but the fingers went right through the fistula and touched the fundus of the bladder. There was fibrous scar tissue surrounding the fistula. The cervix of the uterus could not be felt easily but was adherent to the posterior vaginal wall embedded in scar tissue.

Speculum examination :—A large fistula was seen in the anterior vaginal wall as had been noted by vaginal palpation. The cervix was seen with great difficulty in the posterior fornix, it bled on touch. The ureteral openings were searched for and found in the vault of the vagina. These were verified by anæsthetising the patient with chloroform and passing gum elastic ureteral catheters, and keeping them there. I kept them purposely inside so that they might serve as guides tc the ureters during the subsequent operations.

Preoperative treatment :—The patient was prepared with regular vaginal douching, tonic mixtures, calcium lactate by mouth. One injection of milk 5 c.c. was given for the pelvic cellulitis. The day before the operation ureteral catheters were passed as described above.

Operation :—The operation was performed on the 26th of May 1950. Coffey's operation was decided upon. Plasma was kept ready in case of emergency. Spinal anæsthesia, 15 mg. of anethaine was given. Glucose-saline was started. A midline incision was made. A very high Trendelenberg position was used. The intestines were packed away. There was difficulty in locating the ureters at the pelvic brim, because of the presence of big pelvic blood-vessels. Unluckily the ureteral catheters could not be felt. But after a little time the left ureter was found and dissected out for about 1½". A No. 2 fine rubber catheter was put in and tied in. A flatus tube was inserted through the rectum up to the pelvic brim. The right ureter was similarly dealt with. The flatus tube was drawn out by an assistant, and the rubber catheters were pulled out together with the ureteral ends which lay on the pelvic colon. The ureters together with the rubber tube inside were stitched in the pelvic colon so as to lie in the sub-mucus tissue obliquely as in Witzel's operation. The operation took 2¼ hours to complete. The patient was returned to bed and glucose-saline was administered.

---

* Honorary Surgeon, Civil Hospital, Jalgaon, East Khandesh.

Post-operative course:—The flatus tube was maintained in the rectum. Penicillin and soluseptisine were administered parenterally and sulfadiazine was given by mouth. Powders consisting of urotropine, potassium citrate, and sodium sulphate were given by mouth to act as diuretics and laxatives. The left catheter came out on the 8th day and the right on the 11th day. A rise of temperature on the 12th day was controlled with injections of pyelopurin and glucose.

She developed good control of the rectal sphincter for urine, and was discharged well pleased with the result on the 5th July 1950.

Case II.

A 20 year old female, S. A. was admitted on 1st August, 1950 with a diagnosis of Vesico-vaginal fistula.

History in brief:—A forceps delivery was done two years ago after which she had developed this vesico-vaginal fistula. She was operated on three times without any relief.

Vaginal examination:—There was a big fistula which admitted two fingers.

The patient was prepared with regular vaginal douching and glucose saline injections and calcium injections for fifteen days. Her blood pressure was 95/65.

Operation:—She was operated upon on the 17th August 1950. Exactly the same method was adopted as explained above. It was easily done. Patient was discharged cured on the 13th September 1950.

ACKNOWLEDGMENTS.

Thanks are due to the encouragement given by Dr. Sahasrabuddhe and Dr. Joshi and also for the kind help given by Dr. Acharya, Dr. Chandratrye, Dr. Mrs. Raje and also to the whole nursing staff for the interest and excellent care taken on which depended the success of the operations.

CURRENT MEDICAL LITERATURE

MEDICINE

Bilateral Adrenalectomy in Malignant Hypertension and Diabetes, Green Nelson, Doods, Smalley: J.A.M.A. **144**: 39—443, 1950. 25 references, 6 figures.

Describing a case with fasting blood sugar exceeding 800 mgs. per 100 c.c., and a blood pressure of 270 m.m. systolic and 140 m.m. diastolic, the authors explain how a failure of adaptation to environmental stress landed a girl of six years in diabetes and retarded growth, which culminated, in her adult life in three abortions, malignant hypertension with nephrosclerosis, glomerulosclerosis, encephalopathy and brought her to the verge of heart failure. As the case was otherwise hopeless, the authors undertook to perform bilateral adrenalectomy on the hypothesis that adrenocortical hormones are responsible not only for practically all forms of malignant hypertension, but also for hyperglycemia and glycosuria. There was already much to support this hypothesis, and this case has only added further proof. It was known for long that destruction of the adrenal glands resulted in depression, and hyperplasia in elevation of blood pressure; subsequently it was found that salt-retaining hormones allied to desoxycorticosterone produce a quantitatively proportional elevation of blood pressure and herein really lay the success of empirical treatment of hypertension by salt-depletion. Moreover, these hormones also increase the excretion of glucose in phlorizinised animals, and diminish the reabsorption of glucose by the renal tubules, although it is true that neoglycogenetic fractions of adrenocortical hormones are more potent in producing syndromes resembling diabetes. Fifteen months after the operation the patient was free from attacks of heart failure and encephalopathy; her blood sugar was 98 mg. per 100 c.c. on a total insulin dose of 24 units daily, and her blood pressure ranged from 120 to 150 m.m. systolic, and 70 to 100 m.m. diastolic. It was, of course, necessary to give cortical hormones as substitution therapy for the maintenance of life, and also to keep blood pressure within normal limits. In the course of this substitution therapy, the distinction between the two groups of adrenocortical hormones was clearly brought out: one, the salt-retaining group of hormones allied to desoxycorticosterone which cause elevation of blood pressure, and the other, neoglycogenetic salt depleting lipoadrenal extracts allied to cortisone which do not show such elevating effect on blood pressure. The authors have also performed unilateral adrenalectomy on four other patients for hypertension; one of them died of haemorrhage after operation, another developed a fatal hypertensive encephalopathy, and the remaining two have been running a benign course of the disease.

N. J. Kothari.

Speculations on the Mechanism of Cure of Bacterial Endocarditis, Hunter, T. H.: J.A.M.A. **144**: 524-527, 1950. 7 references, 5 figures and 1 table.

One case of bacterial endocarditis due to the enterococcus-streptococcus liquefaciens, was treated with aureomycin because the organism was sensitive to aureomycin in vitro. The treatment proved infructuous, and the patient died on the 45th day. This led the author to undertake a study of the reaction of this organism to various antibiotics and their combinations. The field of study had to be restricted to *in* *vitro* experiments and clinical experience only, because the organisms which produce sub-acute bacterial endocarditis in man are generally not pathogenic to laboratory animals, and even when one occasionally succeeds in producing bacterial endocarditis in animals, the experimental disease runs a different course in the animals from what it does in man. While biological experiments are not available, it is not possible to depend wholly on *in vitro* experiments because these experiments only provide a measure for the inhibition of bacterial growth, and in no way give any clue as to the number of bacteria actually killed. It is necessary to know this killing action as against mere inhibiting action in treating a case of bacterial endocarditis because in this disease the drug action is not reinforced by the defence mechanism of the body, and the drug itself has to exterminate all bacteria. The organisms find a protected situation in the poorly vascularised vegetations and necrotic valves, where the leucocytes cannot easily reach. This accounts for the failure of spontaneous recovery, and the failure of bacteriostatic drugs like sulphonamides, aureomycin and terramycin, and also the necessity for the protracted treatment with massive doses even of bactericidal penicillin. The authors' experiments gave the following results: (1) Penicillin is bactericidal but cannot effect sterilisation unless aided by other drugs; (2) Aureomycin is only bacteriostatic; (3) Streptomycin has neither action; (4) Combined with aureomycin, penicillin is less effective; (5) Combined with streptomycin, penicillin is more effective; (6) Penicillin alone or combined is effective only during the logarithmic phase of bacterial growth, it is inactive during the other three, namely the lag, stationary and declining phase of bacterial growth; (7) Penicillin becomes ineffective once the growth of bacteria is inhibited by any of the bacteriostatic drugs, aureomycin, chloromycetin or terramycin. The most striking fact which emerged out of these experiments was that streptomycin which by itself has no action on the organisms exercises a synergic action of great potency on penicillin; so much so that the author advances the combination of penicillin and streptomycin as specific therapy for all cases of sub-acute bacterial endocarditis, and thinks that a short course of ten days' duration with this therapy is sufficient to effect a complete cure. Three out of ten patients treated in this way by the author are doing well one month after cessation of treatment.

N. J. KOTHARI.

A NEW METHOD FOR TREATMENT OF BRUCELLOSIS, Herrel, W. E., Barber, T. E., J.A.M.A. **144**: 519-523, 1950: 8 references, 2 figures and 2 tables.

On the basis of their experience with twenty-five patients, the authors advance a plan of treatment for Brucellosis. The plan of treatment consists of the oral administration of 3 gm. of aureomycin hydrochloride per day in divided doses of 750 mg. every six hours, and 1 gm. of dihydrostreptomycin intramuscularly morning and evening during the same period. In the acute bacteremic form and in the acute form with positive culture the treatment is continued for 12-14 days. In cases with localising lesions and positive cultures the same dose of aureomycin orally continued for 28 days, and intramuscular dihydrostreptomycin 0.5 gm. in the morning and 0.5 gm. in the evening for 28 days. The doses of streptomycin suggested do not produce neurotoxic effects on the eighth nerve, provided the renal function is not impaired. It is necessary to administer both drugs simultaneously, and separate courses of the two drugs will defeat the purpose of therapy. Preparations of aluminium hydroxide are contraindicated as they interfere with the absorption of aureomycin. In nine atypical cases of bacteremic form due to Br. abortus, one case of which was confused with rheumatic fever, another with infectious hepatitis, a third with mononucleosis, that were treated by this method ,fever disappeared within 48-72 hours ; and there was no bacteriological or clinical relapse for 19 months. In seven cases of bacteremia due to Br. melitensis, three of whom had signs and symptoms of pneumonia or pneumonitis, only one had clinical relapse after six weeks, and this was accounted for by the interference with absorption of aureomycin by large amounts of aluminium hydroxide which the patient was consuming. All these patients were packing-house workers, and were followed up for 8 to 15 months. In a group of four cases with bacteremia due to Br. suis, where arthralgia was a prominent feature, two recovered completely and had no relapse for 19 months. In one case of bacteremia due to untyped Brucella, which was previously diagnosed as atypical pneumonia, the temperature fell to normal in three days. The incidence of pulmonary symptoms in four cases of Brucellosis shows that it is necessary to perform agglutination tests and blood cultures in all cases of suspected pneumonitis if the patients happen to be occupationally concerned with milk or milk products. There were four cases of Brucellosis with localising lesions, one in the first lumbar interspace, a second in an abscess on the thigh, a third in the lung, a fourth in the groin ; all had a history of previous infection and all were treated and cured in 28 days. In another group of ten cases without positive culture, the same treatment brought the temperature to normal in 42 to 72 hours, but there was a relapse.

N. J. KOTHARI.

DYSPNOEA AS A SYMPTOM OF DISEASE, Wade H. J.: Clinical Journal 79 : 286-290, 1950.

Dyspnoea may be defined as difficulty or distress in breathing or the consciousness of the necessity for increased respiratory effort. This may vary from symptoms noticed by a healthy individual during severe physical exercise to the constant distress experienced at rest by a patient of congestive cardiac failure. The causes of dyspnœa may be classified as follows :—

1. Due to pulmonary disease (a) obstruction of larynx, trachea and bronchi due to lack of oxygen and retention of carbon dioxide. Obstruction due to a foreign body in the larynx, laryngeal diphtheria, œdema of the larynx or pressure on the trachea from outside, (b) the distensibility of the lung is reduced by œdema, congestion, inflammation, fibrosis, pneumothorax pleural effusion, diaphragmatic or intercostal paralysis and by fixity of the chest walls. 2. (a) Cardiac asthma due to hypertension and advanced arteriosclerosis, (b) coronary thrombosis, (c) rheumatic heart disease, (d) congenital heart disease, (e) coronary vascular disease, (f) hypertensive heart disease, (g) thyroid and myxœdema, (h) cardiovasculars yphilis, (i) obesity. 3. In anæmias due to reduced hæmoglobin when such reduction, carries only six volumes percent of oxygen. 4. In raised metabolism hyperthyroi, dism and fever. 5. In nervous disorders, (a) anxiety state, (b) hysteria. 6. Miscellaneous causes; (a) abdominal causes with elevation of the diaphragm, (b) diaphragmatic paralysis, (c) asciteis, (d) tympanits', (e) large abdominal tumours, (f) pneumoperitoneum. 7. Various poisons such as nicotine, lead, alcohol, gases containing carbon monoxide and in acute anaphylaxis. 8. In acidosis, diabetic coma and uræmia. 9. In convalescence after true influenza, virus pneumonia and diphtheria.

J. C. PATEL.

THE CAUSES OF HEMIPLEGIA, Parkinson, J. S.: Clinical Journal 79 : 294-300 1950.

By hemiplegia is meant a condition of impaired function or paralysis of one side of the body due to damage to a pyramidal tract. Hemiplegia has many different causes, from those operating even before birth to those having their effects in old age, with differences in prognosis. Hemiplegia is a syndrome and not a disease and is due to a lesion of one pyramidal tract by various causes at different sites. Hemiplegia will be discussed under various age groups.

1. Arising or evident in the first few years of life (0-4 years): (a) birth injury due to prolonged difficult or precipitate labour or forceps delivery, (b) congenital malformation of the brain, (c) rhesus incompatibility, (d) infections of the nervous systems in infancy, i.e., infectious fever, whooping cough, measles, encephalitis, polio-encephalitis. (e) congenital syphilis. 2. Arising later in childhood (5-15 years): (a) chorea (b) meningitis. 3. Arising in early adult life (15-40 years): (a) disseminated sclerosis, (b) congenital weakness or aneurysm in the wall of a cerebral artery, (c) mycotic aneurysm. (d) syphilitic cerebral thrombosis, (e) intracranial venous thrombosis, (f) thrombophlebitis migrans, (g) epileptic fits. 4. Arising in the forties (40-50 years): (a) syphilis giving general paralysis of the insane or taboparesis, (b) cerebral embolism. 5. Arising in late middle life (50-60 years): (a) cerebral hæmorrhage in a hypertensive patient, (b) cerebral embolism from a recent coronary thrombosis. 6. Arising in the elderly (over 60): (a) cerebral hæmorrhage, (b) cerebral thrombosis, (c) angiospasm, (d) metastatic malignant cerebral deposit. 7. Any age group: (a) cerebral tumour, (b) trauma, (c) subdural hæmatoma.

In conclusion, two other conditions should be mentioned as they superficially mimic. (a) hysteria (b) unilateral Parkinsonism.

J. C. PATEL.

THE NORMAL BLOOD PRESSURE RANGE AND ITS CLINICAL IMPLICATIONS, Master A. M., Dublin, L. I., Marks H. A.: J.A.M.A. **143** : 1464-1470, 1950.

There is very little uniformity as regards the normal blood pressure. Hypertension is a common diagnosis in medical practice and usually bears serious connotation. In this report the authors have examined large numbers of normal persons for establishment in industrial employment, executive, clerical and manual workers, army, airfield and civilian personnel and the results are given from random samples of at least 500 observations for men and women in each group. In the older age group the volume of data was rather small. The normal systolic and diastolic blood readings by age and sex are given in the following table No. 1.

TABLE 1. *Systolic and Diastolic Blood Pressure Readings by Sex and Age.*

Sex and Age ..	Systolic			Diastolic		
	Mean	Stand Dev.	Coef. of Variation	Mean	Stand Dev.	Coef. of Variation
Males						
16	118.4	12.17	10.28	72.9	10.33	14.17
17	121.0	12.88	10.64	74.4	9.36	12.58
18	119.8	11.95	9.97	74.4	10.03	13.48
19	121.8	14.99	12.31	74.6	10.29	13.79
20–24	122.9	13.74	11.18	76.0	9.93	13.07
25–29	125.1	12.58	10.06	77.8	8.98	11.54

Table 1.—(*Contd.*)

Sex and Age	Systolic			Distolic		
	Mean	Stand Dev.	Coef. of Variation	Mean	Stan d Dev.	Coef. of Variation
Males						
30-34	126.1	13.61	10.79	78.5	9.68	12.33
35-39	127.1	14.20	11.17	80.4	10.42	12.96
40-44	129.0	15.07	11.68	81.2	9.53	11.74
45 49	130.0	16.93	13.02	82.0	10.81	13.18
50-54	134.5	19.21	14.28	83.4	11.31	13.56
55-59	137.8	18.80	13.54	84.0	11.40	13.57
60-64	141.8	12.11	14.89	84.5	12.36	14.63
Females						
16	116.1	12.10	10.42	72.3	9.55	13.21
17	116.0	11.51	9.92	72.0	9.16	12.72
18	116.3	11.42	9.82	71.8	8.60	11.98
19	115.1	11.87	10.31	71.1	8.93	12.56
20-24	115.7	11.83	10.22	71.7	9.67	13.49
25-29	116.8	11.43	9.79	73.7	9.05	12.28
30 34	119.8	13.97	11.66	74.9	10.78	14.39
35-39	123.9	13.85	11.18	78.0	10.01	12.83
40-44	127.0	17.07	13.44	79.5	10.60	13.33
45-49	130.6	19.47	14.91	81.5	11.63	14.27
50-54	137.3	21.29	15. 5	83.5	12.36	14.80
55-59	138.5	21.40	15.45	83.5	11.72	14.04
60-64	144.0	22.33	15.51	85.0	12.95	15.24

Mean blood pressure both systolic and diastolic increased with age in both sexes. Average systolic reading for men show a fairly smooth progression up to the age of 50, after that age the increase accelerates. For women the increase in the averages by age is somewhat less smooth or continuous than it is for men, but among them, too, it is accelerated after the age of 50. Beginning with the age of 20 the upward progression in diastolic pressure with age is fairly steady for both sexes.

With the increase in weight there is progressive increase in averages of systolic and diastolic blood pressure regardless of age or sex. There was no relation between the height and blood pressure reading, the normal standard deviation or more from mean, is abnormal. For practical use the range of 5 percent at the upper and lower ends of the graphs may be taken as constituting this normal group. Blood pressure readings which fall in normal range should be considered entirely normal, but those in intermediate zones between this normal range and lower limit of hypertension are best viewed as probably normal but should receive a thorough study before a final decision is reached.

Table No. 6 is reproduced here for showing the limits of hypotension and hypertension.

TABLE 6.—*Normal Range and limits of hypotension and hypertension.*

Age Sex	Systolic*			Diastolic*		
	Hypo-tension Upper Limit	Normal Range	Hyper-tension Lower Limit	Hypo-tension Upper Limit	Normal Range	Hyper-tension Lower Limit
Males						
16	98	105–135	145	52	60–86	90
17	98	105–135	145	55	60–86	90
18	98	105–135	145	55	60–86	90
19	98	105–140	150	55	60–88	95
20–24	98	105–140	150	56	62–88	95
25–29	100	108–140	150	60	65–96	96
30–34	100	110–145	155	60	68–92	98
35–39	102	110–145	160	60	68–92	100
40–44	102	110–150	165	60	70–94	100
45–49	104	110–155	160	60	70–96	104
50–54	105	115–160	175	60	70–98	106
55–59	106	115–165	180	60	70–98	108
60–64	108	115–170	190	60	70–100	110
Females						
16	95	100–130	140	55	60–85	90
17	95	100–130	140	55	60–85	90
18	95	100–130	140	55	60–85	90
19	95	100–130	140	55	60–85	90
20–24	95	100–130	140	55	60–85	90
25–29	98	102–130	140	55	60–86	92
30–34	98	102–135	145	55	60–88	95
35–39	100	105–140	150	60	65–90	98
40–44	100	105–150	165	60	65–92	100
45–49	100	105–155	175	60	65–96	105
50–54	105	110–165	180	60	70–100	108
55–59	105	110–170	185	60	70–100	108
60–64	105	115–175	190	60	70–100	110

* Blood pressure readings in millimeters of mercury.

Blood pressure determination is part of every physical examination, in fact it is too often unduly emphasised. With the spread of voluntary health and accident insurance, with retirement for illness, the concept of range of normal blood pressure will have increased application. The blood pressure standards given in this paper will be useful in a wide sphere of work and future research.

J. C. PATEL.

PEDIATRICS

Chronic Poisoning Due to Excess of Vitamin A, J. Caffey. Pediatrics. 5: 672-688, 1950.

The author describes the clinical and roentgen manifestations in seven infants and young infants who had been given an excess of vitamin A over a long period of time. The morbid anatomy of the lesions is unknown; there have been no biopsies or necropsies.

The estimated daily intake for these patients varied from 75,000 to about 500,000 units of vitamin A. In not one case were these huge doses prescribed by the pediatrician. The parental reasons for giving these large doses of vitamin concentrates varied, some, that a bigger dose would be better, in others that they would combat respiratory infections better, in one that the child had developed a fondness for the vitamin concentrate, and another was unwittingly fed on a vitamin concentrate instead of cod liver oil as prescribed.

There was usually a long latent period of several months between the start of excessive dosage and the appearance of diagnostic signs, this period did not depend on the size of the over-dose. The shortest latent period was 6 months; the longest 15 months. In some cases pruritis and anorexia preceeded clinical signs by several weeks or months. Though enlargement of the liver has been reported, the author has not noticed it in his series. Clinical signs were tender swellings, hyper-irritability and limitation of motion. Swellings were always deep, apparently bony, overlying skin was freely moveable and never edematous. Children were apprehensive and resisted handling. These swellings were most commonly observed in the forearms, but also occurred over the femora, tibias and fibulas, the 2nd, 3rd, 4th, and 5th, metatarsals, the 2nd metacarpals, and clavicles. The jaw and the face were unaffected. Regional lymph nodes were not enlarged. Roentgenographic examination demonstrated cortical hyperostoses occurring in every tender bony swelling which could be detected. The high incidence of localization in the ulnas and metatarsals appears to be a diagnostic feature of hypervitaminosis A. These sclerotic cortical thickenings were gradually resorbed from within, but were visible for several months after clinical recovery. Sometimes they became lamellated. The amounts of vitamin A in the blood were increased in all patients, concentrations varied from 400 to 2,000 u, per 100cc (normal 50-150). These levels fell gradually taking some weeks to return to normal after ingestion of excessive vitamin concentrates were stopped. The most distinctive and convincing features of this syndrome is the rapid and complete clinical recovery after over-dosage is stopped. Tenderness, pain and hyperirritability and anorexia disappeared completely within a week.

The author differentiates hypervitaminosis A, from infantile cortical hyperostosis. Two features are common to both, cortical hyperostosis and tender swellings. Infantile cortical hyperostosis however always appears during the first 4 months of life, fever is the rule, the face and jaw are swollen, the mandible is thickened in every case, scapular lesions more common, metatarsal hyperostosis is rare, blood vitamin A level normal, and the signs and symptoms drag on with exacerbations for weeks or months. Finally, in infantile cortical hyperostosis vitamin intake has not been excessive.

F. A. Nazareth.

Use of Neo-synephrine in Paroxysmal Supraventricular Tachycardia, G, Cunningham and W. Schnitzker: Journal of Pediatrics. 37: 727-732, 1950.

The authors report the intravenous use of neo-synephrine in a child 27 months old admitted with supraventricular paroxysmal tachycardia. It was not possible to say what the tachycardia could be attributed to, but it was postulated that there may have been a congenital cardiac defect, probably an interauricular septal defect. Neo-synephrine was given on three different occasions to this child, the doses being 0.3 mg. on each of the first two occasions; on the third occasion 0.1 mg. and 0.2 mg, were given at intervals of 15 and 20 minutes without effect, but the usual dose of 0.3 mg. brought the heart rate from 220 to 92 beats within 3 minutes. Neo-synephrine seems to act by simultaneous stimulation of the cardiac inhibitory centers: *i.e.*, carotid sinus and aortic arch, by the sudden elevation of the blood pressure. The authors recommend the addition of this drug to the list of medications used in paroxysmal supraventricular tachycardia. Great discretion must however be used as to dosage, as cardiac arrest may occur. As a safe procedure, the authors recommend an initial dose of 0.1 mg. to be increased by 0.1 mg. at intervals of 30 minutes to as high as 0.5 mg.

F. A. NAZARETH.

CARCINOMA OF THE CERVIX IN THE FIRST YEAR OF LIFE, G. HECKEL: PEDIADRICS, 5: 924-929, 1950.

The author reports two cases of adenocarcinoma of the cervix under 1 year of age, making a total of three cases reported so far since Bumm reported the first case in 1909. The reported number of cases of carcinoma of the cervix under the age of 12 is now eight, all adenocarcinomas. Epidermoid carcinoma of the cervix has not been reported under the age of 12. The first of the two cases reported here, aged 7 months was admitted with a history of vaginal bleeding for one month. The child died on the same day of admission. Autopsy showed adenocarcinoma of the cervix extending into the adnexa with metastasis in the retroperitoneal lymph nodes.

The second case was seen at 11 months of age with vaginal bleeding of 4 days duration. Examination of the vagina revealed a friable mass in the vault which was microscopically an adenocarcinoma. Total hysterectomy was performed in preference to roentgen therapy because with the latter the growth of the pelvic bones would be interfered with in addition to the effects of castration. Histological examination showed adenocarcinoma of the cervix, the other organs were normal. A re-check of the patient 1 year after operation showed her in good health. However, abnormal development will doubtless follow removal of the ovaries.

F. A. NAZARETH.

CARDIO-ESOPHAGEAL RELAXATION (CHALASIA) AS A CAUSE OF VOMITING IN INFANTS, W. BERENBERG AND E. NEUHAUSER: Pediatrics 5: 414-419, 1950.

Among the cases of persistent or recurrent vomiting in the new born or young infant, cardio-esophageal relaxation must be borne in mind. In this condition a failure of the gastric cardia to perform its usual 'sphinter' action exists due to a temporary neuro-muscular dysfunction, and in contrast to cardiospasm or achalasia, this syndrome shows persistent relaxation hence termed 'chalasia.'

The patient invariably begins to vomit within 10 days after birth usually within 3 days. It is effortless, rarely forceful or projectile and becomes progressively worse occurring with most feedings, though occasionally some successive feedings are retained. The vomitus does not contain bile. Vomiting is more apt to occur when air is expelled or when the baby is held in the supine position; as a rule vomiting starts with recumbency. Beyond slight malnutrition or dehydration, the baby is otherwise well and reveals no abnormalities. Untreated, the baby either loses weight or gains slowly over a period of many months. An absolute diagnosis can be made by fluoroscopic examination after a barium meal. The esophagus appears larger than usual and looks like a dilated tube leading into the stomach. During inspiration, the intra abdominal pressure is raised and barium from the stomach is pushed into the dilated esophagus; during expiration, the filled esophagus is compressed and some barium is regurgitated into the mouth while some is forced back into the stomach. When the patient is recumbent slight pressure on the abdomen causes regurgitation into the esophagus; crying or struggling will produce a similar picture. No regurgitation takes place when the infant is held erect. Treatment is emperical. Drugs of the atropine and prostigmin group do not alter the clinical course. Feeds have to be thickened with cereal. The infant is kept propped up by the use of pillows throughout the day and night. Some cases required this position for only 30 60 minutes; others were cured by thickening of the feeds alone. On this regimen, vomiting stopped and therapy could be discontinued after 3 to 4 weeks provided there were no central or local causes to perpetuate the vomiting. Repeated roentgenographic studies showed either marked improvement or a normal picture. Four roentgenograms are reproduced to demonstrate this condition.

F. A. NAZARETH.

GEMONAL (5, 5-DIETHYL 1-METHYL BARBITURIC ACID), M. A. PERLSTEIN: Pediatrics. **5**: 448-451, 1950.

Gemonal is a new anti-convulsant drug. It has been shown to possess remarkable anti-convulsant activity against metrozol in cats and mice in doses which produce no sedation. Phenobarbital was found to cause similar anticonvulsant protection in the same dosage but caused greater sedation.

The author records a preliminary experience with this drug in 50 cases of epilepsy. Gemonal was supplied in a 0.1 Gm. scored tablet. The patients varied in ages from 4 months to 64 years, the average age being about 8 years. The dosages of Gemonal varied from 0.02 to 0.18 Gm. given one to four times daily for periods ranging from one week to three years. The dose prescribed usually was 1½ to 2 times that of phenobarbital. In a total of 58 instances, benefit was noted in 21 and no benefit in 37. Of 32 cases with grand mal, 9 were improved; of 14 cases with petit mal, 4 were improved; in 11 cases of myoclonic spells, 8 were benefited. In 35 cases of epilepsy associated with organic brain disease, there was improvement in 18 cases; in the remaining 15 cases of idiopathic epilepsy, only in one case was improvement noted.

It would appear that Gemonal was most effective in the myoclonic forms of epilepsy and in epilepsy due to organic brain disease. Gemonal is relatively non-toxic; in only one case was a morbilliform rash observed; no blood changes have been observed so far. It appears to be valuable as an adjuvant or alternate drug where other drugs have failed to control seizures.

F. A. NAZARETH.

Indian Journal of Medical Sciences
(INCORPORATING THE MEDICAL BULLETIN)

VOLUME 5 MARCH 1951 NUMBER 3

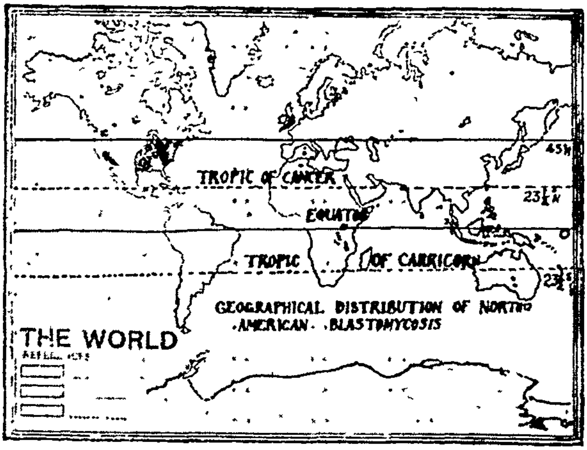
COPYRIGHT BY THE INDIAN JOURNAL OF MEDICAL SCIENCES

BLASTOMYCOSIS IN INDIA

REPORT OF A CASE

H. S. Andleigh *

Fungus infections in India may be of common occurrence but excepting the dermatophytes, the actinomyces and rhinosporidium infections, the other types of fungus infections are usually not identified. Even cases of dermatophytes and other mycotic infections which are of common occurrence are sparingly referred to the pathologist. It is difficult to understand why cases of fungus infections other than those commonly seen and reported should not occur in India. It may be that they occur but are not identified probably because we take little interest in mycology. Medical mycology has no place in the undergraduate curriculum of the Medical Colleges in India. As the subject is rather difficult and not very interesting it has little attraction even to those who undertake post-graduate training. It is, therefore, possible that cases of fungus diseases hitherto not reported may be occurring in India but have remained unidentified.



Map showing geographical distribution of Blastomycosis.

---

* Department of Pathology, S. M. S. Medical College, Jaipur.

CASE REPORT.

P. K. Hindu male, aged 44 years, resident of Jaipur since birth and never been out Jaipur.

Married, wife alive and healthy.

Children three—living and healthy. Two died of common ailments.

Denies any history of venereal diseases.

He is an adult of sober habits and does not drink or indulge in any intoxicants.

History of present Illness.—About 20 years back the patient noticed a small raised papule-like eruption on the inner side of the left thigh near the junction of upper and middle thirds. The patient received some medicinal treatment which lasted for 2 years resulting in partial cure. The lesion then assumed the form of a small ulcer but there was no discharge of any frank pus from the ulcer. The condition remained like this for many years, sometimes improving after treatment and sometimes deteriorating. The condition for the last four years has been increasing almost continuously, the extension being peripheral to the original ulcer. A number of minute abscesses appeared along the margin and kept on appearing with the increase of the lesion. About a year back, active treatment with several lacs of penicillin given four hourly improved the condition but soon after the penicillin was stopped, the original condition returned with innumerable minute drops of pus at several points in the granulation tissue. The pus was slightly thick in consistency and yellowish white in colour.

The Lesion.—The lesion at the time of present examination extended over an area of about 6 inches in length and 3 inches in breadth. The surface was irregular with granulation tissue and a raised edge, ending abruptly into healthy skin. At a number of points particularly at the margin of the lesion many abscesses were present from which pus could be pressed out in small beads.

Systemic examination of the body did not reveal anything abnormal in any other part of the body.

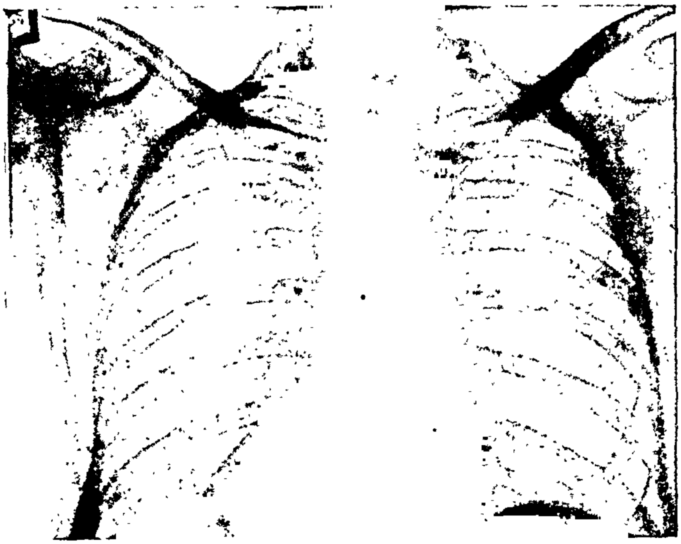
X'Ray Findings.—Roentgenogram of the left femur did not show any bony lesion. Roentgenogram of the chest showed dense hilar shadows and some calcified nodes in the hilar region. The rest of the pulmonary fields were clear. Mediastinal silhouette was heavy.

Laboratory Examinations ·

1.	BLOOD	Hæmoglobin percentage	70% (Sahli).
		Total R.B.C.	3,200,000 per c.mm.
		Total W.B.C.	8,500 per c.mm.
		Polymorphonuclears	78%
		Lymphocytes	18%
		Large monocytes	2%
		Eosinophils	2%
		Erythrocyte sedimentation rate (Westergren)	½ hr.—15 mm. 1 hr.—35 mm.
2.	URINE	Specific gravity	1018
		Reaction	Acidic.
		Albumin	Nil.
		Sugar	Nil.

Microscopic:

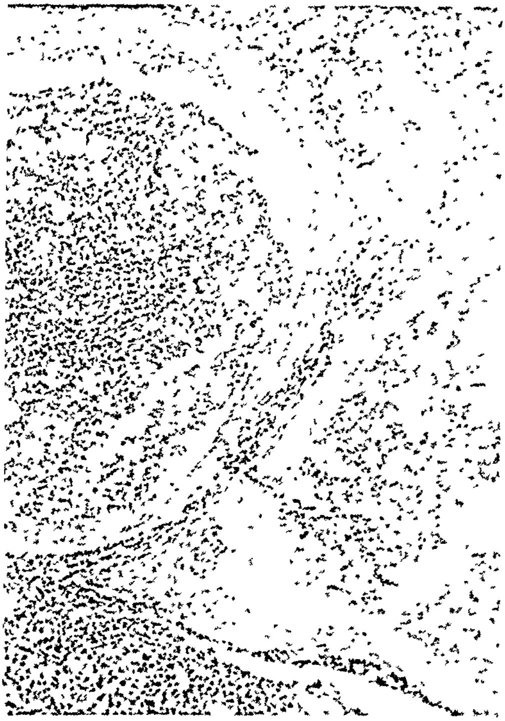
No casts.
No crystals of amorphous urates present.
No red blood cells or pus cells seen.



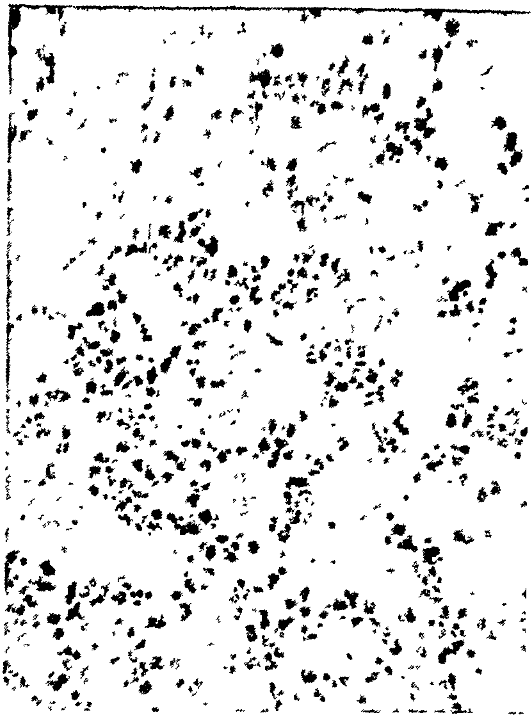
2. Skiagram of the chest showing dense hilar shadows and a few calcified nodes in the hilar region.

3. Skiagram of left femur showing no bony lesion.

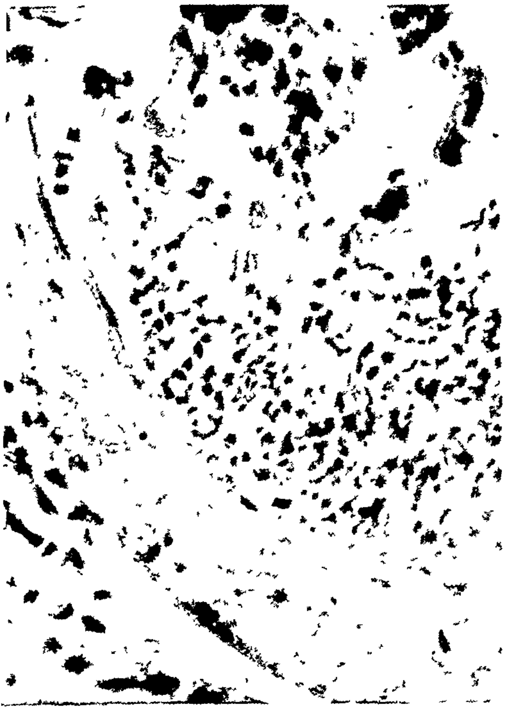
4. Photograph of the case showing the lesion.



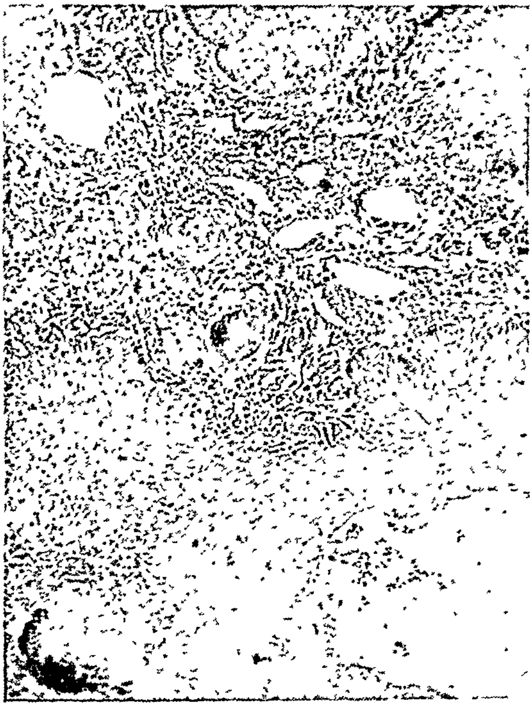
5. Section showing Blastomyces in the miliary abscesses.



6. Section showing doubly contoured Blastomyces dermatitidis.



7. Section from another site showing Blastomyces.



8. Section from another site showing giant cells.

3. *The Discharge from the Lesion.*—Microscopic examination of the discharge of pus from the lesion showed the presence of yeast-like cells with refractile doubly-contoured cell wall. Budding was not very evident except in one or two cells where not more than a single bud projecting out of the parent cell could be seen. The morphology of the cells very much resembled that of *Blastomyces dermatitidis.*

Microscopic examination of the stained smears showed pus cells and some secondarily infecting organisms of the nature of gram-positive cocci. Here and there a large yeast-like cell was present, but it was difficult to say if it was *Blastomyces dermatitidis.*

4. *Cultural Examination.*—Pus was cultured on Sabouraud's medium and blood agar. On Sabouraud's glucose agar at room temperature the growth appeared in 4 days time. The colonies were somewhat glabrous and moist. They were of a whitish colour. Microscopic examination of the growth showed small broad mycelia which were thick walled and closely septate. Conidia were rarely seen and those seen were rather oblong or oval in shape.

On blood agar at 37° C growth appeared in 5 days' time. The colonies were more or less tan in colour and of a worm-cast type.

Microscopic examination of a smear from such a colony showed some cells which were spherical or circular and had a doubly-contoured looking cell wall, but this character was not seen in all the cells. Some cells were oval, long and thick.

The pathogenicity of the culture could not be tested for lack of facilities.

Biopsy Examination.—A small piece of tissue from the lesion was cut for histopathological examination which showed a portion of the epidermis and dermis. There was marked hyperkeratosis and dyskeratosis, with occasional formation of large squamous pearls. In the epidermis, within the stratum corneum were several abscesses, some confluent. The abscesses showed a debris of epithelial cells and a fair number of inflammatory cells ; there was a preponderance of neutrophils together with a few lymphocytes and macrophage cells. In a few of these intra-dermal abscesses were seen rounded cyst-like bodies about 15-20 microns in diameter. They had a thick double-contoured faintly acidophilic wall and contained a little irregular lump of basophilic (nuclear) material within the cyst cavity. Sometimes two smaller clumps were seen. No budding cysts could be found in several sections examined.

The stratum malpighi showed marked proliferation of cells and the formation of irregularly inter-connected branching retecones. In some areas there was a loss of cell polarity and frequency of mitosis simulating a malignant change. The subjacent connective tissue showed chronic inflammatory granulation tissue. Areas of necrosis were present. There were numerous dilated and engorged capillaries. Several areas showed extravasation of blood. The cellular exudate was composed mainly of plasma cells and lymphocytes as well as a fair number of neutrophils.

The presence of dermal abscesses with a neutrophilic exudate, as well as the cystic organisms found in them suggest a cutaneous lesion of North American Blastomycosis.

Intradermal Tests.—0.1 c.c. of Blastomycin (1 in 1000) was injected intradermally into the left forearm and 0.1 c.c. of Coccidioidin (1 in 100) was injected intradermally into the right forearm. Both the injections were given simultaneously. The reactions were read at the end of 48 hours. There was an erythematous induration on the left forearm measuring 6.5 mm., in diameter and that on the right forearm measured 3 mm. only.

Complement Fixation Test—The complement fixation test could not be done on account of a lack of facilities.

CONCLUSIONS

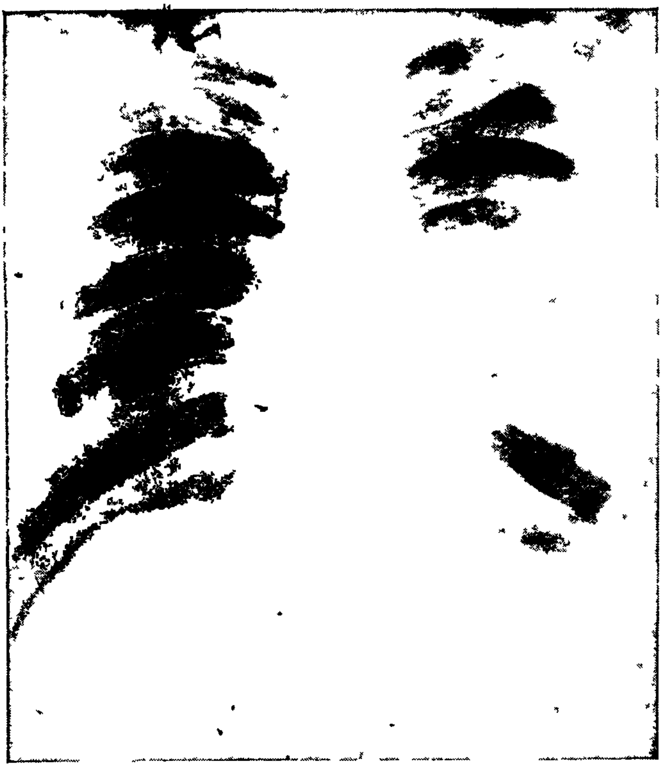
It appears from the clinical history of the case and from the laboratory examinations that this case is one of Primary Cutaneous Blastomycosis. The other condition from which it has to be differentiated are coccidioidomycosis and lupus. It cannot be coccidioidomycosis as no endospores could be seen and also the Coccidioidin test was negative. The histo-pathological findings are against lupus. The chronicity of the case, the presence of doubly-contoured yeast-like cells in the discharge from the lesions and in the tissues, the presence of minute satellite abscesses in the skin and a positive Blastomycin test go to show that this is probably a case of Primary Cutaneous Blastomycosis. The fact that such a case has never been reported in India should not be taken for holding the idea that such cases cannot and do not occur in India. From the climatic point of view, cases of blastomycosis and coccidioidomycosis have been reported from the areas of the United States of America, which lie between the same parallels in the north as the part of India to which this case belongs.

ACKNOWLEDGMENT.

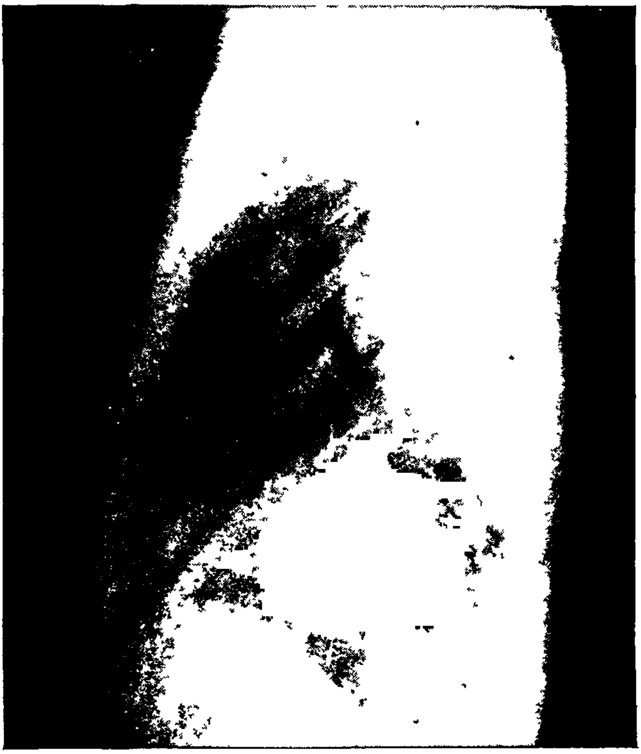
My thanks are due to Dr. V. R. Khanolkar, Bombay for confirming my findings of the sections and to Dr. P. N. Wahi, Agra for very kindly providing me with Blastomycin and Coccidioidin for intradermal tests. My thanks are also due to Dr. M. P. Mathur, Dermatologist, S. M. S. Hospital, Jaipur for valuable help in the clinical examination of the case.

REFERENCES.

1. Baker, R. D.: Tissue reactions in Human Blastomycosis, Am. J. Path. **18**: 479, 1942.
2. Benham, R. W.: The fungi of Blastomycosis & Coccidioidal granuloma, Arch. Dermatol Syphilol, Chicago, **30**: 385, 1934.
3. Callaway, J. L. & Mosley, V.: Primary Cutaneous Gilchrists Disease, So. Med. J., **33**: 622, 1940.
4. Conant, N. F.: Manual of Clinical Mycology. W. B. Saunders Co., Philadelphia, 1945.
5. Henrici, T.:—Molds, Yeasts & Actinomycetes. John Wiley & Sons. Inc. New York, 1947.
6. J. E. Ash & S. Spitz.; Pathology of Tropical Diseases—an Atlas W. B. Saunders Co., Philadelphia, 1945.
7. Lewis, G. M. & Hopper M. E.: An Introduction to Medical Mycology. (The Year Book Publications.) 1948.
8. Ormsby & Montgomery.: Diseases of the Skin, Henry Kimpton, London 1948.



1. Primary Actinomycosis of the Lung. Skiagram of Chest-posterior anterior view.



2. Primary Actinomycosis of the Lung Skiagram of Chest-left lateral view.

PRIMARY ACTINOMYCOSIS OF THE LUNG

M. N. Rananavre*

Primary Actinomycosis of the lung presents many difficulties in its clinical diagnosis, firstly because it simulates common lung affections such as tuberculosis, pneumonia, abscess etc., and the possibility of actinomycosis of the lung is often completely neglected and secondly, the laboratory investigations cultural, immunological or animal inoculations are not always reliable because of the fact that certain situations, such as carious teeth, tonsillar crypts and apparently even the normal mouth serve as permanent reservoirs of pathogenic fungi. Under these circumstances, we rarely come across patients whose conditions are diagnosed as primary mycotic infections of the lungs, specially where there is no secondary spread to the thoracic wall or elsewhere. This latter often settles the true nature of the primary condition in the lungs, as exemplified in the following case report.

Case History

A male, 32 years old, a medical graduate and a general practitioner of Poona, was in a good state of health till the 10th October, 1948. On this day he had fever and pain over the lower left intercostal region without any physical signs in the lungs. After three days his temperature (maximum 101° F.) came down to normal and the pain disappeared. One evening, in the last week of November, 1948 he got drenched to the skin in rain and on the following day he started getting a pain in the back about the angle of the left scapula, with a sensation of chill. During the next four days the pain increased in severity, and the physical examination showed an impaired note and deficient air entry over that area. (max. temp. 100° F.) Total W. B. C. 10,000 with 67% polymorphs. On screening a round opaque patch was seen about the middle of the left lung. The condition was diagnosed as (?)unresolved pneumonia and treated as such. In the following week he developed a cough with expectoration, more marked at night, the sputum being occasionally rusty.

The sputum was examined (24 hours collection) twice but was negative for acid fast bacilli.

On a second fluoroscopic examination at the end of two weeks, the size of the pneumonic patch was found to be much reduced and it was more transparent.

He was in a satisfactory state of health till the 8th February, 1949, when the same old symptoms viz., pain, fever, and cough with expectoration returned, with impaired note, deficient air entry and a definite pleural rub over the left scapular region. On the 16th February, a radiograph of the lungs showed a triangular opacity with indefinite borders in the middle of the left lung. This appearance (in conjunction with the basal soft systolic murmur in the heart) was thought to be due to an infarction of the lung. On the 17th February for the first time, frank blood was noted in the sputum. The condition of the patient became worse, and on the 22nd February screening of the chest showed hydropneumothorax, which

---

Department of Pathology, B. J. Medical College, Poona.

was not there in the radiograph taken only 6 days earlier. The patient never had any acute pain in the chest during this period to suggest the sudden occurrence of spontaneous pneumothorax.

The report of the radiological examination runs as follows: "A moderately dense but fairly homogeneous opacity is seen in the middle zone of the left hemithorax in the postero-anterior views. The opacity shows crowded vascular lung markings, with normal overlying vascular shadows. The opacity is diffuse superiorly but is sharply demarcated below by a dense arched margin which is convex upwards. Below this arched margin there is evidence of air in the pleural cavity surmounting a horizontal fluid level; fairly thick shadows of thickened pleura merge above and below into the main mid-zone opacity. The various views show that the hydropneumothorax lies mainly at the postero-lateral aspects and that there is collapse of the left lower lobe, the collapse being incomplete, as there are pleurodiaphragmatic adhesions antero-medially and also at the axillary and postero-axillary aspect of the chest wall. It is impossible to assess the condition of the incompletely collapsed lung at the present stage and there are no appearances to suggest the presence of tubercular infiltration but it is possible that the pneumothroax may be due to the existence of an old healed primary tubercular focus."

On 28th February, 1949, probably due to exertion, he vomited blood, and for the next few days the sputum was streaked with blood. The sputum was examined histologically for evidences of a neoplasm and tuberculosis, both with negative results. The patient's general condition improved under penicillin therapy but he had three major relapses during the month of March and December 1949 and May 1950. All these subsided after rest and penicillin administration. During every relapse the condition of the lungs was checked radiologically and a radiograph taken in the month of June 1950 did not show any fluid or air in the pleural cavity, the lung having returned to its original size. There was no appreciable change in the mid-zone opacity. Until now he had taken about 40,000,000 units of penicillin and a small amount of sulphonamide drugs and irgafen tablets. During this period the disease was variously diagnosed as acute tuberculosis, congenital cystic disease, unresolved pneumonia, infarction, and abscess of the lung.

The final act in this long drawn out episode began in the first week of June 1950, when the swelling appeared over the left 8th, 9th and 10th ribs below the angle of the scapula. The swelling was very painful, oval in shape 3″+4½″ in size, firm in consistence, bony hard in the centre with indefinite borders and in connection with the 9th and 10th ribs. The skin over the swelling was freely moveable; total white blood cell counts 12000 with 80 per cent. polymorphonuclears. The radiograph of the ribs did not show any abnormality in connection with the ribs. The pain increased in severity and the temperature remained hectic (maximum 102 F.). By the 15th of June 1950 the skin over the swelling was oedematous and red and no fluctuation was elicited. A diagnostic aspiration was done and only a few flakes of inspissated pus were removed. When examined bacteriologically the pus was found to be sterile. Following this aspiration both pain and temperature increased. Therefore on the 6th August, 1950, under general anaesthesia the skin over the swelling was incised and a thorough excision of the necrotic mass was undertaken; the ribs were healthy. The histological examination of the biopsy material from the abscess wall showed the ray fungus in the midst of chronic granulomatous tissue. The wound healed gradually leaving behind only a small raw area with a sinus. The general health of the patient at present, is satisfactory enough to enable his return to work, except for pain in the left subcostal region after meals due to the pleuro-diaphragmatic adhesions and a moderate rise in the body temperature towards evening.

Previous illness:—(1) Very weak in infancy and childhood; suspected congenital heart disease. (2) Tonsillectomy 1926. (3) Haemoptysis? 1934. (4) Electrocardiogram normal in 1938. (5) Renal colic in 1942 and again during the present illness; stone not detected by X-ray examination.

DISCUSSION

The lung is considered as the primary site of the actinomycotic infection for the following reasons: (1) Absence of any other obvious primary focus in the body. (2) Detection of the pleural adhesions to the posterior wall of the thorax after radiological examination on 23-2-49. This was probably the beginning of the spread into the chest wall by contiguity. (3) The radiological and the laboratory investigations do not substantiate any other diagnosis.

It is generally agreed now, that actinomycosis is caused by *A. bovis* (Harz, Wolff, and Israel). The situations like carious teeth, tonsillar crypts, act as reservoirs from which infection may spread to the lungs especially when the local as well as general resistance of the patient is lowered due to any cause. In the present case the devitalizing factors may be traced to the past illness of the patient with the added habit of rather heavy smoking. "A predisposing allergic sensitization of the host is a theory which has its supporters".[1] The significance of haemoptysis in 1934 in relation to the present illness is doubtful. "It is quite likely that the actinomycotic infection is superimposed upon a primary tubercular affection of the lung".[2]

The prompt recognition of the disease is essential as delay in beginning treatment may result in a fatal outcome. In this instance the patient's lung affection remained obscure and perplexing for over a period of 1½ years. Such a long period might have proved fatal in the absence of penicillin administration. A total of 40,000,000 units of penicillin did not prevent spread of the disease to the chest wall. It could be inferred, therefore, that yet larger doses should be given in order to check the further growth of the fungus.

"There is no pathognomonic syndrome by which a given case could be recognised as bronchomycosis. Suspicion is sometimes entertained when it is a question of chronic pulmonary condition which by its symptoms and physical signs suggest tubercular infection and at the same time, granules, yeast cells, mycelium or spores are demonstrated in the sputum with or without *Mycobacterium tuberculosis*. The specific diagnosis however, is arrived at through careful considerations of the microscopic evidence, as well as cultural results, without neglecting case history, occupation, or other antecedent or concomitant significant infection. Reliance on sputum examination alone may be misleading and has no justification".

CONCLUSION

In presenting this case history, it is intended that all chronic and obscure lung affections be investigated for mycotic infection along with other causes. It is urged that the mycotic infections of the lung are not so rare as they appear to be from hospital records.

SUMMARY

This is a case report of Primary Actinomycosis of the lungs. The condition was diagnosed only after the histological examination of the tumour-like mass that appeared on the chest wall.

I am indebted to Drs. S. R. Joglekar, F.R.C.S., Nanavati and Major A. C. W. Dessa, I.A.M.C., for their valuable help in the preparation of this paper.

REFERENCES

1. Gohar, N. Mycoses and Practical Mycology, 1948.
2. Gollerkeri. Personal communication.
3. Lewis and Hopper. An introduction to Medical Mycology, 1948.

STUDIES IN B-COMPLEX METABOLISM

THE INFLUENCE OF THIAMINE AND RIBOFLAVIN ON THE LIVER FUNCTION IN HUMAN SUBJECTS

R. G. Chitre* and **B. Y. Nadkarni***

INTRODUCTION

The importance of thiamine and riboflavin in human nutrition has now been fully recognised. Attempts were, therefore, made by different workers to assess the nutrition level of an individual—as regards these vitamins—by different methods.

The nutritional level has been assessed by many authors by noting the urinary excretion of thiamine and riboflavin [1], [4], [5], [6], [8], [9], [19], [20], [23], [25], [28], [30] and [32]. From their findings, it is noted that there is a wide variation in the normal urinary excretions of these substances. According to these workers the excretion of thiamine in normal human subjects ranged from 60 to 1327 µg in 24 hours, and that of riboflavin from 236 to 4401 µg in 24 hours.

The relationship of these vitamins to other body functions has also been a subject of detailed investigation. The work done on this aspect by various workers has been reviewed by Bicknell *et al* [3].

The importance of individual members of the B-complex in normal liver function has not been clearly understood. It has been shown that *choline has an intimate relationship with some of the liver* diseases [7], [14], [17], and [24]. Favourable results were reported by Patek[21] and Patek and Post [22] in the treatment of clinical hepatic cirrhosis by means of a highly nutritional diet supplemented with B-complex. Working on similar lines Bharucha, Chitre and others[2] have shown that there is a lowering of liver function in vitamin B-deficiency, the degree of liver dysfunction depending upon the acuteness of the deficiency state. They have further shown that there was a sharp change towards normal in the impaired liver function, when the patients were given large doses of thiamine and riboflavin and niacin in the form of B-complex. This was followed by a disappearance of deficiency symtoms.

In the present work an attempt has been made to find the exact relationship of thiamine and riboflavin with the liver function by noting the excretion of these vitamins in the urine of deficient individuals, at varying levels of intake.

---

* Biological Section, Department of Physiology, Seth G. S., Medical College, Bombay.

EXPERIMENTAL

The patients selected for study all showed clear symptoms of B-deficiency such as edema of the extremities, nervous disorders, feeling of 'stomach congestion', pellagra and oral lesions. Each patient was screened to ascertain the absence of other unrelated diseases. On admission each patient received liberal supplements of vitamins A, C, & D, for two days, casein hydrolysate (50 cc. of 5 per cent solution intravenously, daily) for 3 days and the juice of two sour limes and hospital cod liver oil mixture daily throughout their stay, by way of excluding the probability of any deficiency other than that of the B-complex. The diet maintained was standard hospital diet with appropriate proportions of carbohydrate, fat and proteins, providing 2000 calories (approx.)

The majority of the subjects were between the ages of 15 and 45 years as can be seen from the Histogram (Fig. I).

Age distribution of the subjects

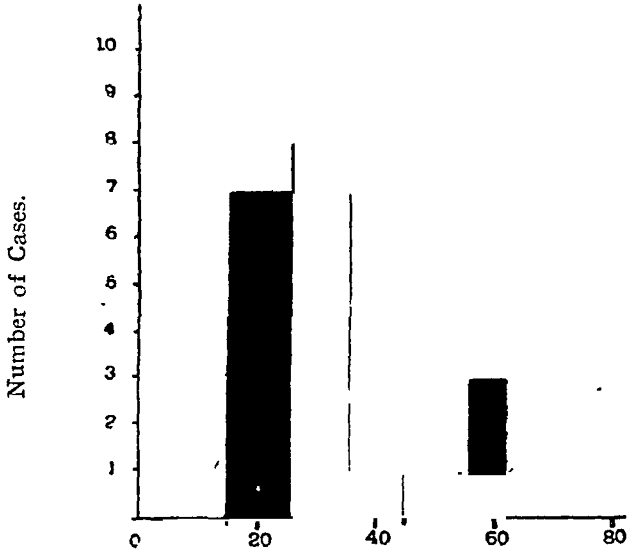


Fig. I Age (years)

The first sample of a 24-hour collection of urine was saved on the 4th day with 20 c.c. glacial acetic acid, and thiamine and riboflavin assayed in it to find the basal excretion of these vitamins. Simultaneously the liver function of each patient was studied using four different tests, *i.e.*, (i) Cephalin Cholesterol test[13], (ii) Thymol turbidity test[15] by using gelatin standards for measuring turbidity, (*iii*) Brom-sulphalein test[29] and (iv) Bilirubin excretion test[31]. Thiamine was estimated fluorometrically by the method of Holman[12] and Riboflavin, by the method of Najjar[18].

TABLE I

Twenty four hour urinary excretion of thiamine and riboflavin in the subjects with signs of vitamin B-deficiency.

Case No.	Age	B_1 µg.	B_2 µg.	Case No.	Age	B_1 µg.	B_2 µg.
1	30	..	672	14	28	35	84
2	28	..	454	15	45	nil	nil
3	62	29	321	16	40	nil	151
4	40	29	274	17F	35	nil	82
5	24	nil	156	18	28	44	nil
6	23	61	442	19	60	74	491
7	25	47	330	20	40	nil	nil
8F	35	nil	34	21	15	20	66
9	18	39	141	22	20	nil	nil
10	40	21	262	23	23	nil	378
11	35	123	3000	24	45	nil	234
12	26	38	276	25	45	nil	126
13	58	nil	51	26	47	nil	135

F = Female.

The patients were then given high doses of thiamine and riboflavin in the form of B-complex injections (see tables) for a period of 3 days. On the last day each patient was asked to save the 24 hours' urine and thiamine and riboflavin estimations were performed to study the levels of saturation. The liver functions tests were also carried out at this stage as before.

RESULTS AND DISCUSSION

(a) *Thiamine and riboflavin excretion in deficient individuals:*

Almost in all cases the clinical findings of a deficiency state seemed to have been confirmed by the low excretion values of thiamine, and in some cases, of riboflavin (Table I). Case 11, however, showed a fairly high excretion of thiamine and riboflavin although clinically the case was one of B-complex deficiency. The excretion of thiamine ranged from 0 to 74 µg in 24 hours, the majority of the cases excreting between 0 to 40 µg (Table II); the excretion of riboflavin ranged from 0 to 672 µg and the majority of cases excreted between 0 to 200 µg (Table III). In the case of riboflavin a large number of cases have shown a strikingly high

TABLE II.

Twenty four hour urinary excretion of thiamine and riboflavin in the subjects with liver function estimations:

(Dose: 25 mg. B_1 and 5 mg. B_2).

Case No.	B1 mg.	B2 mg.	Liver Function Tests							
			Basal				On saturation			
			C.C.	T.T.	Brom	Bili	C.C.	T.T.	Brom	Bili
3	7.8	1.2	1+	4	0.0%	0.7%	1+	4	0.0%	1.0%
4	0.69	1.2	1+	4	0.0%	0.2%	+—	4	0.0%	1.5%
5	6.88	1.8	1+	3	1.0%	1.5%	+—	6	1.2%	2.5%
6	5.68	1.4	1+	6	2.0%	2.0%	>1+	6	1.2%	1.6%
7	1.56	1.7	2+	8	8.3%	2.7%	1+	5	0.0%	1.5%
13	3.65	0.65	2+	10	2.0%	2.5%	<2+	8	1.6%	2.0%

Normal values for the liver function tests:—

C.C.—Cephalin Cholesterol	No flocculation or +—.
T.T.—Thymol Turbidity	3 to 4 Units.
Brom.—Bromsulphalein	No retention.
Bili.—Bilirubin	No retention.

24 hours'excretion of thiamine in deficient subjects.

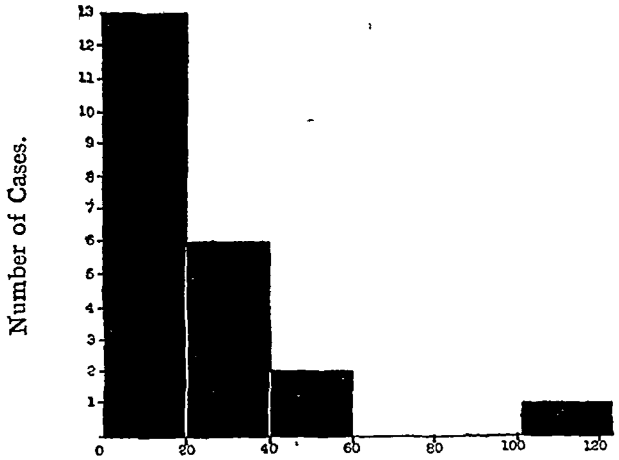


Fig II Micrograms

excretion of the vitamin, though they showed signs of clinical deficiency of the vitamin. Najjar and Holt[20] also observed that the B_2-deficient cases studied by them excreted 24 to 119 μg daily. Similar observations have been reported by Hagedorn *et al*[10] and Hathaway and Lobb[11] who have noted large excretions of riboflavin in B_2-deficient cases. The high excretion of riboflavin in some cases might also be

24 hours' excretion of Riboflavin in deficient subjects.

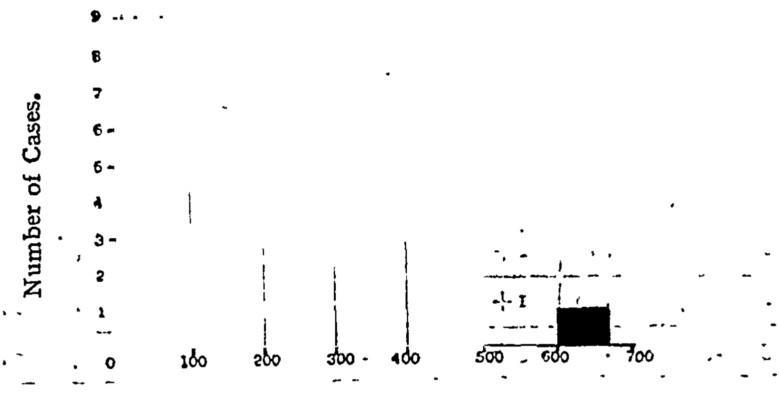


Fig III Micrograms

explained on the basis of the relation of thiamine deficiency to riboflavin excretion, as pointed out by Sure[26] and Sure and Ford[27]. Michelsen and his associates[16] also reported similar findings. The liver function of these cases also showed deficiency on the basis of one or more criteria employed.

(b) *Thiamine and riboflavin excretions on saturation with the following dose:* 25 *mg.* B_1 *and* 5 *mg.* B_2.

It seemed from the excretion of thiamine and riboflavin in Table II that this dose had slightly improved the condition of the patients, as is also seen from liver function tests. But it still appeared that the patients were capable of utilising higher amounts of thiamine and riboflavin since about 80 per cent of the thiamine and 74 per cent of the riboflavin in the dose given were retained by the patients. Cases 4, 7, and 13 especially appeared to be more deficient as seen from their excretions. This was probably due to the low saturation in these cases on admission (Table I). In this group many of the subjects showed liver function improvement on the basis of at least one of the criteria employed (Table V).

(c) *Thiamine and riboflavin excretions on saturation with the following dose:* 50 *mg.* B_1 *and* 5 *mg.* B_2.

In this group the average retention of thiamine and riboflavin was about 70 per cent in almost all cases (Table III). When one scrutinized these cases from the view point of excretion, it could be seen that the cases 12, 16, 17, 18, and 21 have reached a good level of saturation. Cases 1, 15, 24, 25 and 26 are next in the order. The liver function of most of these cases have shown improvement in more than one criteria (Table V). The cases 19, 20, and 22 did not appear to be well saturated as is seen from their low excretions after the dose; this again will probably be due to the low level of saturation in these cases on admission (Table I).

TABLE III

Twenty four hour urinary excretion of thiamine and riboflavin in the subjects with liver function estimations :—

(Dose : 50 mg. B_1 and 5 mg. B_2)

Case No.	B1 mg.	B2 mg.	Liver Function Tests							
			Basal				On saturation			
			C.C.	T.T.	Brom	Bili	C.C.	T.T.	Brom	Bili
1	12.4	1.9	1+	10	1%	1.5%	1+	9	1%	4%
12	27.7	1.06	1+	9	1.7%	2%	1+	8	1.2%	1.7%
15	13	1.4	3+	9	1.7%	2%	<2+	7	0.4%	0.7%
16	17.7	0.443	1+	6	0%	1%	+—	5	0%	0.4%
17	18.9	1.9	+—	4	0.4%	0.6%	+—	4	0%	0.4%
18	24.9	2	1+	5	0.3%	0.5%	+—	4	0%	0.2%
19	1.25	0.54	2+	10	2%	3%	2+	8–9	1.7%	2%
20	4.2	1.2	>1+	6–7	0.3%	1.2%	>1+	6–7	0.3%	1.8%
21	24	1.9	2+	10	0.6%	0.7%	2+	10	0.6%	1.5%
22	7.8	0.54	2+	9	0.4%	1.2	2+	8–9	0.4%	1%
23	8.5	2.3	1+	6	0.4%	0.8%	+—	5	0%	0.6%
24	12.6	1.1	<1+	5	0%	0.6%	+—	4	0%	0.3%
25	11.2	2.2	<1+	5	0.5%	1%	+—	5	0.4%	0.8%
26	10.5	1.5	1+	4	0.7%	<1%	1+	4	0%	0.8%

TABLE IV

Twenty four hour urinary excretion of thiamine and riboflavin in the subjects with liver function estimations :—

*(Dose : 80 mg. B_1 and 16 mg. B_2)**

Case No.	B1 mg.	B2 mg.	Liver Function Tests							
			Basal				On saturation			
			C.C.	T.T.	Brom	Bili	C.C.	T.T.	Brom	Bili
8	79.2	13.7	1+	7	1.6%	2.5%	1+	5	1.3%	2%
9	49.6	8.9	>1+	8	1.3%	1.8%	1+	6	0%	1%
10	55.6	5.5	1+	6	1.1%	1.5%	+—	5	0%	0.5%
11	62.4	0.32	2+	10	1.6%	2.2%	1+	7	0.6%	1.1%

* The dose was given as :—50 mg. B1 and 1 mg. B2—Injection and 30 mg. B1 and 15 mg. B2—oral (tablets).

TABLE V

Showing improvement in liver function of each case on administration of graded doses of thiamine and riboflavin.

Case No.	C.C.	T.T.	Brom	Bili	Remarks
Dose : 25 mg. B1 and 5 mg. B2					
3	—	—	—	—	Improvement in 13 places out of 24.
4	|	—	—	—	
5	|	—	—	—	
6	|	—	|	|	
7	|	|	|	|	
13	|	|	|	|	
Dose : 50 mg. B1 and 5 mg. B2					
1	—	|	—	—	Improvement in 36 places out of 56.
12	—	|	|	|	
15	|	|	|	|	
16	|	|	—	|	
17	—	—	|	|	
18	|	|	|	|	
19	—	|	|	|	
20	—	—	—	—	
21	—	—	—	—	
22	—	—	—	|	
23	|	|	|	|	
24	|	|	|	|	
25	|	—	|	|	
26	|	|	|	|	
Dose : 80 mg. B1 and 16 mg. B2					
8	—	|	|	|	Improvement in 15 places out of 16.
9	|	|	|	|	
10	|	|	|	|	
11	|	|	|	|	

— No improvement.
| Definite improvement.

(d) *Thiamine and riboflavin excretions on saturation with the following dose:* 80 *mg.* B_1 *and* 16 *mg.* B_2.

From the excretions of the subjects under this dose, it seemed that they were in a fair state of saturation, except case 11 which showed unusual excretions before and after the dose (Table I and IV). No valid explanation could be given for this peculiar behaviour. The liver function also showed a greater degree of improvement as indicated by the tests (Table V).

From the above findings it could be seen that there was a close relationship between the vitamins of the B-complex and liver functions. The importance of two of the members (thiamine and riboflavin) other than choline, in the liver function is also evident from the studies. More so because, there was seen an interesting gradation of improvement in the liver function which could be correlated with the amount of the dose.

SUMMARY

1. Twenty six patients showing signs of B-deficiency have been investigated. Their 24 hours' urinary excretions of thiamine and riboflavin and the liver function were studied prior to saturation with these vitamins.

2. The patients were divided into three groups and given graded doses of thiamine and riboflavin. After a fixed period on these supplements, they were reinvestigated for the excretions of these vitamins in the urine, and for the liver function.

3. It was observed that there was an improvement in the liver function in all the doses studied, but the extent of improvement varied directly with the amount administered.

4. The study pointed out that thiamine and riboflavin also play an important part in the liver function of an individual.

BIBLIOGRAPHY

1. Axelrod A. E., Spies T. D. and Elvehjem C. A.: A study of urinary riboflavin excretion in man, J. Clin. Invest. 20 : 229, 1941.

2 Bharucha, E. P., Chitre, R. G., Golwalla A. F. and Nadkarni B. Y.: Liver function and the vitamin B-complex, Ind. Physician 8 : 113, 1949.

3. Bicknell, F. and Prescott, F.: The vitamins in Medicine. Second Ed. William Heinemann, Medical Books Ltd. 1946.

4. Carden, G. A., Province W. D., and Ferrebee J. W.: Clinical experiences with the measurement of the urinary excretion of vitamin B1, Proc. Soc. Exper Biol. Med. 45: 1, 1940.

5. Davis, M.—The excretion of riboflavin by young women on several levels of intake, Thesis, 1945.

6. Feder, V. H., Lewis, G. T., and Alden, H. S.: Studies on the urinary excretion of riboflavin, J. Nutrition **27**: 347, 1944.

7. Fouts, P. J.: Vitamin B-complex studies in dogs; production of cirrhosis of liver, J. Nutrition **25**: 217, 1943.

8. Goodhart R.: The thiamine content of human blood and urine as determined by the fermentation method, J. Clin. Invest. **20**: 625, 1941.

9. Guha, R. C. and Bashir Ahmad: Observations on the vitamin B1 excretion of four healthy subjects living on different Indian diets, Ind. J. Med. Res. **27**: 465, 1939.

10. Hagedorn, D. R., Kyhos E. D., Germe, O. A. and Sevringhaus E. L.: Observations on riboflavin excretion by the adult male, J. Nutrition **29**: 179, 1945.

11. Hathaway, M. L., and Lobb, D. E.: A comparison of riboflavin synthesis and excretion in human subjects on synthetic and natural diets, J. Nutrition **32**: 9, 1946.

12. Holman, W. I. M.: A new method for the oxidation of Aneurin to thiochrome and a procedure for the determination of Aneurin in oats, Biochem. J. **38**: 388, 1944.

13. Krautman, B.: Microcephalin cholesterol flocculation test on blood from finger Am. J. Clin. Path. **16**: 127, 1946.

14. Lowry, J. V. *et al.*: Treatment of dietary liver cirrhosis in rats with choline and casein, Pub. Health Rep. Wash. **56**: 2216, 1941.

15. Maclagan, N. F.: Thymol turbidity test; new indicator of dysfunction, Brit. J. Exper. Path. **25**: 234, 1944.

16. Michelsen O., Doeden D., and Keys A.: The urinary excretion of riboflavin by man as related to diet and physical activity, Fed. Proc. **4**: 98, 1945.

17. Miller, L. L. and Whipple, G. H.: Liver injury, liver protection, and sulphur metabolism. Methionine protects against chloroform liver injury even when given after anaesthesia, J. Exper. Med., **76**: 421, 1942.

18. Najjar, V. A.—The fluorometric determination of riboflavin in urine and other biological fluids, J. Biol. Chem. **141**: 355, 1941.

9. Najjar, V. A. and Holt, L. E.: Studies in thiamine excretion. Bull. J. Hop. Hosp. **67**: 107, 1940.

20. Najjar, V. A. and Holt, L. E.: A riboflavin exceretion test as a measure of riboflavin deficiency in man, Bull. J. Hop. Hosp. **69**: 476, 1941.

21. Patek, A. J. Jr.: Treatment of alcoholic cirrhosis of liver with high vitamin therapy, Proc. Soc. Exper. Biol. Med. **37**: 329, 1937.

22. Patek, A. J. and Post, J.—Treatment of cirrhosis of liver by nutritious diet and supplements rich in vitamin B-complex, J. Clin. Invest. **20**: 481, 1941.

23. Rama Sastri B. V., Mukundan R., and Patwardhan, V. N.: Studies on the urinary excretion of riboflavin and thiamine in Indian adults, Ind. J. Med. Res. **38**: 3, 1950.

24. Rao, P. K.: Infantile cirrhosis of liver, Proc. Ind. Acad. Sc. **14**: 310, 1941

25. Robinson, W. D., Melnick, D. and Field, H.: Urinary excretion of thiamine in clinical cases and the value of such analyses in the diagnosis of thiamine deficiency, J. Clin. Invest. **19**: 399, 1940.

26. Sure, B.: Vitamin interrelationships, J. Nutrition, **27**: 447, 1944.

27. Sure, B. and Ford, Z. W.: Vitamin inter-relationships. J. Biol. Chem. **146**: 241, 1942.

28. Swaminathan, M. : Fluorometic estimation of riboflavin in urine, Ind. Jour Med. Res. **30**: 37, 1942.

29. Todd, J. C. and Sanford, A. H. : Clinical diagnosis by laboratory methods Ed. 10. P. 428, W. B. Saunders Co. 1943.

30. Wang, Y. L. and Yudkin, J. : Assessment of the level of nutrition. Urinary excretion of aneurin at varying levels of intake, Biochem. J. **34**: 343, 1940

31. Weech, A. A., Vann, D. and Grillo, R. A. : The clearance of bilirubin from the plasma. A measure of the excretion power of the liver, J. Clin. Invest. **20**: 323, 1941.

32. Williams R. D., Mason, H. L., Cusick, P. L. and Wilder, R. M. : Observations on induced riboflavin deficiency and riboflavin requirement of man, J. Nutrition **25**: 361, 1943.

THE EOSINOPHILIC RESPONSE IN CASTRATES AND NON-CASTRATES

O. T. Samani; M. M. Gertler; J. B. Hamilton and P. D. White. *

A review of literature reveals observations and studies on circulating eosinophils in diverse conditions from the time of Erhlich's description at the end of the last century. Erhlich named the leucocytes, whose coarse granules had a special affinity to eosin and other acid dyes, as "eosinophiles."

Eosinopenia has been reported in a few conditions such as following injection of splenic extract (Drennan *et al*[11] 1930), after electrically induced convulsions in man (Alschule[1] 1949), following epinephrine, insulin, and surgical operations (Almy and Laragh[2] 1949); by adrenalin infusion and insulin hypoglycemia (Godloski[15] 1948).

Total absence of eosinophils in circulating blood in 5 out of 20 cases of general paralysis of insane cases has been reported (Jelliffe[19] quoted by J. Ewing 1903).

That the number of circulating eosinophils is influenced in a definite way by the state of endocrine balance, particularly the adrenal cortex, is indicated in results of experiments which show that the number of circulating eosinophils changes after a single injection of 25 mg. of purified adrenocorticotropic hormone in normal subjects and patients with Addisonian disease (Thorn *et al*,[37] 1948). Eosinopenia of 50 per cent. or more, following this procedure, has been suggested as indicating adequate cortical reserve of hormones regulating carbohydrate, fat and protein metabolism. Using 0.02 mg. of adrenalin, by injection, per 100 gms. of body weight and studying its effect on adrenal cholesterol and ascorbic acid in experimental animals, it is proved that such procedure (in experimental animals) causes stimulation of anterior pituitary with increased secretion of ACTH, which in turn, stimulates the adrenal cortex(Long and Fry[27] 1945). Assuming the possibility of the same mechanism in humans, it is reasonable to suggest that an injection of adrenalin causes the stimulation of the anterior pituitary with increased secretion of ACTH which in turn, stimulates the adrenal cortex; which in turn, knocks out circulating eosinophils by increased secretion of 11 oxy-steroids (and not desoxycorticosterone, since only 11 oxy-steroids influence eosinophils). (Medical Annual 1949). Long *et al*[27] (quoted by Recant, Horsham and Thorn, 1948), in previous studies, have demonstrated a rapid fall in circulating eosinophils in man by a sudden increase in adrenal 11. 17 oxy-steroids.

---

* From Coronary Research Project, Massachusetts General Hospital, Boston, Massachusetts, U. S. A.

Castrates, both in animals and men, have been studied from various other angles (Joedicke[20], 1919), (Lipschutz[26], 1924), (Ellison and Wolff[13], 1934-1935), (Winter and Emery[40], 1936), (Lawless[25], 1936), (Deansley and Parkes[9], 1937), (Korenchevsky *et al*[24], 1937), (Hall and Korenchevsky[17], 1938), (Kenyon *et al*[22], 1937), (Zeckwer[18], 1938), (Hamilton[18]. 1948). Studies on eunuchs and Skopecs (McCartney[28], 1929), (Rowe[33], 1933), and on eunuchs (Koch[23], 1921), (Wagenseil[39], 1927), (McCullagh and Renshaw[29], 1934), have also been reported.

The present study is concerned with observations on circulating eosinophils in (a) human male castrates before and after a subcutaneous injection of adrenalin hydrochloride, and (b) observation of normal controls in the same institution in otherwise identical experimental conditions.

MATERIALS AND METHOD

Twenty-five male castrates were studied (Table I). They were castrated on account of their mentally defective states in order to prevent further procreation. Their present ages ranged from 17 years to 67 years. The number of years after birth when castration was performed ranged from 8 years to 37 years, body weights ranged from 109 to 221 pounds, and heights ranged from 151.9 cm. to 182 cm.

Another group of 19 men from the same institution were studied as normal controls (non-castrates) (Table II). Their present ages ranged from 15 years to 37 years, body weights ranged from 91½ pounds to 226 pounds, and heights ranged from 157.5 cm. to 180.4 cm.

Both groups were subjected to the following test of eosinophilic response. No food was taken after 10;00 p.m., the night prior to the test. An initial circulating eosinophil count was done next morning at 7 : 30 a.m., according to the method described by Thorn *et al*,[36] 1948. Then, without breakfast, a single injection of 1 : 1000 adrenalin chloride (0.5 cc per square meter surface area) was administered. At 11:30 a.m., four hours after the injection by which time the circulating eosinophils show maximum fall (Thorn *et al*, 1948), an eosinophil count was done again, following the above mentioned technique.

RESULTS

I *Results of the eosinophilic response in both the castrates and non-castrates*

The results of the eosinophilic response in both the castrates and non-castrates are summarized in Tables I and II. Table I (castrate group) reveals another observation which may be significant. There are six subjects which show murmurs in the heart. The three cases (Nos. 5, 17, and 21) which show rheumatic valvular heart disease show an initial eosinophil count of 639, 716 and 516 cells per cu. mm., res-

TABLE I.

CASTRATES.

No. of Cases.	Age.	Number of eosinophil cells per cu. mm. prior to adrenalin inj.	Same count after adrenalin inj.	Percentage decrease.	Number of years after birth when castration performed.	B.P. in mm. Hg..	Other Remarks.
1	17	75	12	83.3	16	120/60	
2	24	125	16	87.34	9	124/76	
3	23	300	84	72.02	17	116/72	
4	20	153	69	55.10	15	106/72	
5	23	639	312	51.10	16	120/42	Pre-syst. murmur & mid diast. murmur apex: aortic regurg. rheum. heart disease.
6	29	216	86	60.14	24	140/82	
7	26	328	152	53.81	17	130/66	
8	24	453	5	89.66	16	110/82	Large protruding umbilicus.
9	24	94	30	68.33	15	130/96	Rh negative.
10	26	59	12	78.95	17	115/68	Syst. murmur gr. 2-early. 2nd left int-space near sternal border: pre syst. M. Apex. No. DM after exercise.
11	31	494	126	74.37	16	114/92	Rh negative.
12	31	77	8	83.87	28	90/60	
13	36	20	9	53.85	18	..	
14	38	33	11	66.67	22	134/84	
15	36	39	8	80.00	27	150/96	
16	36	88	50	42.86	24	98/80	Kyphoscoliosis-Erb's paralysis rt. arm—due to birth injury
17	33	716	238	66.81	23	122/62	Syst. mur. gr ^{2} mid diast. rumble—apex.
18	34	136	38	72.41	19	150/84	

* Rheumatic fever

TABLE I.

CASTRATES—(*Contd.*)

No. of Cases.	Age.	Number of eosinophil cells per cu. mm. prior to adrenalin inj.	Same count after adrenalin inj.	Percentage decrease.	Number of years after birth when castration performed.	B.P. in mm. Hg.	Other Remarks.
19	47	44	6	85·71	34	106/76	Funnel chest. Syst. murmur at apex
20	42	97	36	62.95	26	110/72	Syst. murmur gr. 1 apex
21	42	516	17	66.67	26	110/74	Syst. murmur gr. 2 apex and pulm. area—Rh negative.
22	55	127	27	79.01	37	152/86	
23	53	178	20	88.60	31	156/90	
24	62	53	32	38.24	8	142/86	Slight rheumatoid arthritis.
25	67	81	28	65.38	13	136/92	

* Rheumatic fever.

TABLE II.

NORMAL CONTROLS (NON-CASTRATES)

No. of Cases.	Age.	Number of eosinophil cells per cu. mm. prior to adrenalin inj.	Same count after adrenalin inj.	Percentage decrease.	B.P. in mm. Hg.	Other Remarks.
1	18	373	112	69.87	124/84	Syst. murmur gr. 1, apex and pulm. area
2	17	61	8	87.18	110/66	
3	18	173	134	22.52	120/62	Syst. murmur gr. 1, apex
4	18	262	112	57.14	122/75	Syst. murmur gr. 1., apex
5	19	30	0	1000.00	108/60	(?) Gallop rhythm.
6	17	619	161	73.99	114/80	Tonsils out
7	15	120	6	94.81	116/62	Syst. murmur gr. 1, pulm. area
8	19	330	50	84.83	116/78	Large lymphadenoid pharynx. Rosenmuller
9	25	317	33	89.66	122/82	
10	29	114	33	71.23	128/72	Syst. murmur gr. 1, apex
11	24	375	9	97.50	125/82	S. M. gr 1, apex. Undescended testis. Deformity left leg.
12	22	675	172	74.54	124/68	S. M. gr. 1 apex & mid sternum. Fainted N. C. A.
13	21	230	34	85.03	136/70	Tonsils absent. Syst murmur gr 1, apex
14	20	373	47	87.45	120/64	Residul tags of tonsils
15	25	234	38	84.00	122/82	Syst. murmur, gr. 1, apex
16	26	295	89	69.84	154/92	Possible Cushing. Striae on abdomen
17	22	236	8	96.69	120/84	Tonsil tags
18	20	145	45	68.82	126/75	Inguinal and umbilical hernia.
19	37	461	78	83.05	132/82	Gallop rhythm—auricular sound at apex

*Rheumatic fever.

pectively (higher than 500), while the highest similar count from the other four murmur cases (which are apparently functional murmurs) is 96.87 cells per cu. mm. It is not possible to comment on this particular observation since the series is small, and only three cases of rheumatic heart disease are encountered in the control series for use as comparisons. Further studies along these lines are indicated.

II. *Initial eosinophil counts and response to adrenalin injection*

The results are summarized in Tables I and II. The castrate group, on an average, showed a lower eosinophil count per cu. mm. as compared with the average eosinophil count of the control group.

The overall results are summarized in Table III below.

TABLE III

	Av. eosinophil cell count per cu. mm. before adrenalin inj.	Av. eosinophil cell count per cu. mm. after adrenalin inj.	Absolute decrease per cu. mm.	Percentage decrease
Castrates	148.63	39.32	109.32	70.0
Non-Castrates (control) ..	229.25	47.37	181.88	79.06

The percentage decrease in the case of the castrate group was about 9 per cent less than that of the normal control. Thus, there is a uniform disparity both in initial count and in response to adrenalin injection in these two groups of cases. There is no definite relation between the initial eosinophilic count or the percentage decrease in the eosinophils with either increasing age in either group or the age at which castration was performed.

DISCUSSION

The statistical difference in the initial eosinophilic count between the castrates and non-castrate groups requires explanation. The effect of the following factors known to affect the eosinophilic count may be dismissed, for they were constant in both groups: (a) hunger, (b) fear and pain associated with the test, (c) morning temperature, (d) diurnal variations, and (e) other psychological factors. The initial difference in eosinophil counts between the two groups may best be explained on an hormonal basis. Whether this observation is due to (a) a diminution of androgens, (b) a relative increase in estrogens, or (c) action on the adrenal cortex via the pituitary, the extent to which some of these factors affect the following physiological changes are still moot questions :

(a) the sites of eosinophil production, (b) the mechanism of destruction, (c) the redistribution of the eosinophils in the system, (d) the normal physiological properties of the eosinophils.

The most striking feature in this study is the significantly lower eosinophilic count in the castrate group in contrast with the non-castrate group. This is important in the light of work of Shands, Bartler, and Pincus who have found that the initial eosinophillic count is lower in females as compared with males. The castrated group are genetic males and hormonally non-males and closer akin to the females as observed from voice changes, fat accumulation and skin changes, although Zappert[41] failed to demonstrate from his extensive studies any uniform sex differences in eosinophilic count. There is theoretical evidence in favour of the viewpoint of Shands *et al* in that the adrenal glands in females in many species are heavier in contrast with the adrenal glands of males of similar species (Donaldson[10], 1924), (Cole and Harned[7], 1942), (Deanesly[8], 1938), (Bennett[3], 1940). The exception to this rule is found in pigeons (Riddle[32], 1923).

It is known that estrogens have a stimulating effect on the adrenals and pituitary glands in mice (Burrows[6], 1936), rats (Golla and Reiss[16], 1941), (Selye and Albert[35], 1942), on guinea pigs (Tuchmann[38], 1936), and on chickens (Breneman[5], 1942). While activation (increased rate of hormonal production) is not necessarily synonymous with hypertrophy, it is reasonable to suggest that the adrenal glands of the castrates are at least activated if not hypertrophied. Two observations favour this view: (*a*) activation of the adrenals is greater with a moderate dose of estrogen in contrast with a larger dose (Bourne and Zuckerman[4] 1940). (b) There is virtually no opposition in the castrates to the circulating estrogens by androgens. An additional observation which indirectly supports the view that in castrates the adrenals are constantly being stimulated by circulating estrogens, is the increased protein catabolism observed after castration in male rats (Sandberg[43] *et al*—1939); a situation not unlike that met with in the castrate group as judged by the excess accumulation of fatty tissue.

The low initial level of circulating eosinophils 2 to 20 cells per cu. mm. in Cushing's syndrome in contrast with normal subjects (Thorn *et al*—1948) is evidence in favour of destruction of eosinophils by the adrenal cortical hormones. Accordingly, it is reasonable to suggest, on the basis of the evidence, both direct and indirect, cited in this paper, that the eosinophil count is lower in the castrates in contrast with the controls because of the relative preponderance of estrogen level in their blood.

There is considerable attention at present on the possible role of ACTH and adrenal cortical hormones in the rheumatic fever reported in this communication. The eosinophil count was statistically higher in contrast even with the highest count of the other cases. It is possible that, in these individuals, there was a diminished secretion of 11 oxy-ketosteroids in spite of the overall normal adrenal cortical reserve.

SUMMARY

(1) Basal eosinophil counts were taken on 25 male castrates, castrated at ages varying from 9 to 37 years. For comparison, similar counts were taken on 17 individuals of comparable age, from the same institution who were not castrated.

(2) The initial eosinophil count in the castrate group averaged 148.63 cells per cu. mm. Similar count in non-castrate group averaged 229.25 cells per cu. mm.

(3) The eosinophil count in the castrate group decreased 109.32 cells per cu. mm., four hours after adrenalin injection while the similar decrease in non-castrates showed 181.88. The percentage decrease in eosinophil counts of both groups was normal and virtually the same, 70 per cent in castrate and 79.06 per cent in non-castrate groups.

(4) A discussion on the significance of the eosinophil in the castrate group is considered.

ACKNOWLEDGMENTS

Thanks are due to Dr. C. C. Hawke, Medical Director, and Mr. L. Tune, the Managing Director, of the State Training School in Winfield, Kansas, for their co-operation in making available the clinical material.

REFERENCES.

1. Alschule, M. D., Parkhurst, B. H., Tilloston, K. J.: Decreases in Blood Eosinophilic Leukocytes after Electrically Induced Convulsions in Man, J. Clin Endocrin. **9**: 440, 1949.
2. Almy, T. P. and Laragh, J. H.: Am. J. Med. April, 1949.
3. Bennett, H. S.: The Life History and Secretion of the Cells of the Adrenal Cortex of the Cat, Am. J. Anat. **67**: 151, 1940.
4. Bourne, G. and Zuckerman, S.: Changes in the Adrenals in relation to the normal and artificial threshold oestrous cycle in the Rat, J. Endocrinol. **2**: 283, 1940.
5. Breneman, W. R.: Action of Diethylstilbestrol in the Chick, Endocrinology **31**: 179, 1942.
6. Burrows, H.: Changes induced by oestrogens in the Adrenals of Male Mice, J. Path and Bact. **43**: 121, 1936.
7. Cole, V. V. and Harned, B. K.: Adrenal and Pituitary weights in Rats with Reduced Glucose, Tolerance, Endocrinology, **30**: 146, 1942.
8. Deanesley, R. and Parkes, A. S.: Multiple activities of Androgenic Compounds, Quart. J. Exper. Physiol. **26**: 393, 1937.
9. Deanesly, R.: Nature **141**: 79, 1938.

10. Donaldson, H. H.: Mem. Wister Institute of Anatomy & Biology. No. 6, 1924.

11. Drennan, A. M. and Biggart, J. H.: Persistant Eosinophilia, J. Path. and Bact. 33 : 995, 1930.

12. Engelbach.: "Endocrine Medicine" Thomas, Springfield and Baltimore, 1932.

13. Ellison, E. T. and Wolff, J. M.: Effect of Castration on the Anterior Hypophysis of Female Rat, . Endocrinology 18, : 555, 1934. Changes in Anterior Hypophysis of the Male Albino Rat after Castration and Experimental Cryptorchism, Endocrinology 19 : 160, 1935.

14. Ewing, J.: Clinical Pathology of Blood, Lea Brothers and Co. 1903.

15. Godlowski, Z. Z.: Eosinopenia caused by adrenaline infusion and by insulin Hypoglycaemia, B. M. J. 1: 46-48, 1948

16. Golla, Y. M. L. and Reiss, M. (Introduced by J. H. Gaddum) Observations on Adreno-Cortico Trophic Action—From The Burden Neurological Institute, Stoke Lane, Stapleton, Bristol. J. Physiol. 100, : 1. 1941.

17. Hall, Kathleen and Korenchevsky.: Effects of Castration and of Sexual Hormones on the Adrenals of Male Rats, J. Physiol. 91, : 365, 1938.

18. Hamilton, J. B.: Recent Progress in Hormone Research Vol. 3, 1948.

19. Jelliffe (Quoted by J. Ewing, 1903).

20. Joedicke, P. Z. ges. Neurol. Psychiatry. 44 : 385—390, 1919.

21. Jolly.: Traite technique d'hematologie. 1923.

22. Kenyon, A. T., Gallagher, T. E., Peterson, D. H., Dorfman, R. I. and Koch, F. C.: The urinary excretion of Androgenic and Estrogenic Substances in Certain Endocrine States, Studies in Hypogonadism Gynecomastic and Virilism, J. Clin. Investigation. 16 : 1706, 1937.

23. Koch, W. Uber die eussisch rumanische. Kastraten sekte der Skopzen G. Fischer Jena. 1921.

24. Korenchevsky, V., Marjorie Dennison and Margaret Eldridge.: The Effects of Δ^4 Androstenedione and Δ^5 Androstenediole on Castrated and ovariectomised Rats, Biochem J. 31, : 467, 1937.

25. Lawless, J. J.: Castration in the Rat with and without removal of the Epididymis, Anat. Rec. 66, : 455, 1936.

26. Lipsochutz. The Internal Secretion of Sex Glands—Heffer. Cambridge 1924.

27. Long, C. N. H. and Fry, E. G.: Effect of Epinephrine on Adrenal Cholesterol and Ascorbic Acid, Proc. Soc. Exper. Biol & Med. 9, : 67, 1945.

28. McCartney, J. L.: Dementia Precox as an Endocrinopathy with Clinical and Autopsy Reports, Endocrinology, 13. : 73, 1929.

29. McCullagh, E. P. and Renshaw, J. F.: The Effects of Castration in the Adult Male, J. A. M. A. 103, : 1140-1143, 1934.

30. Medical Annual—John Wright & Sons, Bristol, England, 1949.

31. Recant, Lillian, Forsham, P. H., and Thorn G. W.: Observations on Pituitary Adrenal Response following Epinephrine Infusion in Man, J. Clin. Endrocrinol, 8 : 589, 1948.

32. Riddle O.: Studies on the Physiology of Reproduction in Birds. Suprarenal Hypertrophy coincident with Ovulation, Am. J. Physiol. 66, : 322, 1923.

33. Rowe.: "Differential Diagnosis of Endocrine Disorders" Williams & Wilkins— Baltimore, 1933.

34. Sandberg, M., Perla, D., Holly, O. M.: Effect of Castration in Albino Rats on Nitrogen Sulfur Chloride Sodium and Potassium Metabolism and on Changes in Weight and Food Intake, Endocrinology. 24, : 503, 1939.

35. Selye, H. and Albert, S.: Age Factor in Responsiveness of Pituitary and Adrenals to Folliculoids., Proc. Soc. Exper. Biol. & Med. 50 : 159, 1942.

36. Thorn, G. W., Forsham, P. H., Prunty, F. T. G., Hills, A. G.: J. A. M. A. 137,: 1005—1009, 1948.

37. Thorn, G. W., Forsham, P. H., Recant Lillian, Hills A. G.: The Use of Adrenocorticotropin as a test of Adrenal Cortical Reserve, J. Clin. Endocrinol. 8 : 589, 1948.

38. Tuchmann, H.: Compt. rend. Soc. de Biol. 122, : 1239, 1936.

39. Wagenseil, F. Z.: Morphol Anthropol. 26, : 264—304, 1927.

40. Winter, C. A. and Emery, F. E.: Compensatory Adrenal Hypertrophy in the Rat as influenced by Sex, Castration, Time, and Thyroidectomy, Anat. Rec. 66, : 401, 1936.

41. Zappert. Ziet-f-Klin. Med. 1902.

42. Zeckwer, I. T.: The Effect of Combined Thyroidectomy and Gonadectomy on Compensatory Adrenal Hypertrophy in Unilaterally Adrenalectomized Rats, Am. J. Physiol. 123 : 266, 1938.

TRAUMATIC FEMORAL ARTERIOVENOUS FISTULA.

Report Of A Case

V. P. Mehta.

Case Report

D. L., a factory worker aged 32 years was admitted to the King Edward VII Memorial Hospital on the 15th June, 1949 complaining of eczema and swelling of the right lower extremity.

Present Illness:—The patient noticed a swelling of the right foot in June 1945, which gradually involved the whole leg causing difficulty and pain on movement of the affected limbs.

Past History:—He had a sore on the penis in 1929. In 1942 he had received a stab wound in the right femoral region. He was referred to the hospital by a physician for treatment of "varicose veins" and ulcer.

Physical Examination :—Examination showed a well developed and well nourished, alert, co-operative patient.

Leg:—The right lower extremity was markedly swollen. The skin of the lower part of the right leg was eczematous and showed marked varicosity of the veins in the right thigh and gluteal region, extending down the whole leg. A continuous thrill with systolic accentuation was felt in the right femoral region. Auscultation revealed a loud continuous bruit with systolic accentuation, audible over the course of the femoral vessels. There was a scar of a stab-wound, a little below the right anterior superior iliac spine. Branham's sign was positive. The pulse rate slowed by 8 beats with pressure on the aneurysm.

Heart:—The left border of the heart was outside the mid-clavicular line in the 5th left intercostal space. The heart sounds were of good quality with a systolic murmur heard all over the precordium. The pulse rate was 84 and water hammer in character. The blood pressure was 106 mm. Hg. systolic, and 50 diastolic.

Laboratory Studies:—Examination of the urine showed a specific gravity of 1024, no albumin and no sugar. Microscopic examination showed 3 white blood cells and no casts per high power field. The red blood cell count was 4,800,000 per cmm. with a haemoglobin content of 13 Gm. per 100 cubic centimeters. The blood Kahn Test was positive(++++).

Diagnosis:—A diagnosis of traumatic arteriovenous fistula between the right femoral artery and vein was made.

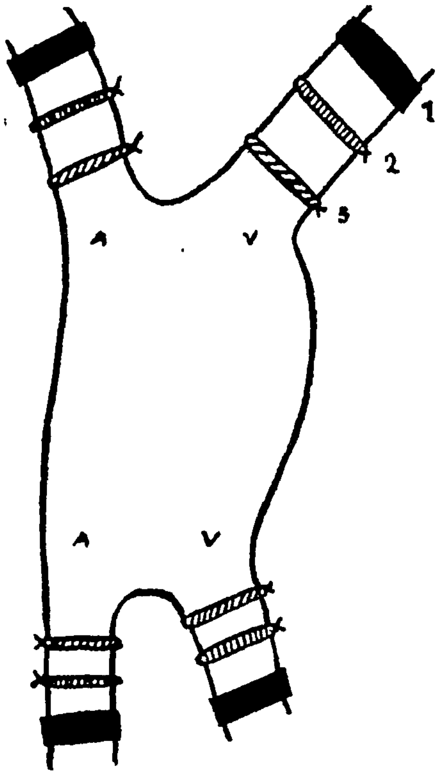
Pre-operative Treatment.—The patient was given penicillin.

Operation:—On the 20th June, 1949, under endotracheal ether anaesthesia, a vertical incision was taken over the femoral triangle and later extended horizontally medially in the lower end. The incision was deepened cautiously and the many bleeding points encountered were caught and immediately a diathermy current applied to them. The Poupart's ligament was cut to facilitate exposure of the femoral vessels in the upper part. The femoral vein was markedly dilated with thick arterial walls and showed pulsation. The thrill was conducted for a short distance upward into these vessels and could be obliterated by fingerpoint compression over the proximal end of the femoral artery. The vessels were well isolated after cutting the sheath and a tape was passed round each one separately and held up without tying. The same procedure was now carried out after isolating the vessels in the lower part and tapes passed round them well below the thrill. All these four points were ligated with tape and Deknatel sutures were used as follows :—

---

* Hon. Assistant Surgeon, King Edward Memorial Hospital, Bombay.

The aneurysm itself was now carefully isolated. The profunda and other vessels were now seen feeding the aneurysm from behind. They were ligated, transfixed and cut. The sac was thus freed. Clamps were now applied between the main four feeders and the sac was then excised. The stumps were re-inforced with an additional transfixion ligature using Deknatel black silk. The wound was closed with No. 10 linen mattress sutures. The brachial blood pressure fell from 140 mms. to 100 mms. of mercury during the operation but went back to the original level shortly after ligature of the main femoral trunk.



1. TAPE
2. LIGATURE WITH DEKNATEL SILK
3. TRANSFIXION LIGATURE WITH-DEKNATEL SILK

Post-operative Course:—Oozing occurred from the wound and the limb felt heavy and without sensation for the first twenty-four hours but the next day it was warm and the swelling of the leg had considerably reduced on the third day. Stitches were removed on the sixth day when the wound showed gross infection. It healed sixteen days later after treatment with local and parenteral penicillin.

When the patient was discharged, the leg had returned to its normal size, varicose veins had disappeared, the ulcer had healed, the eczema was better and the patient could walk very comfortably.

Follow-up:—The patient has been followed up for a period of one year. The wound has healed completely and the leg has returned to its normal size.

COMMENT.

This case had one definite advantage from the operative point of view *viz.*, the long duration of four years of the arteriovenous fistula allowed sufficient time for enough collateral circulation to develop. Most surgeons are agreed that the best time to operate is between the third and sixth month after the injury.[1] In this case the longer duration favoured a better collateral circulation but carried with it the risk of cardiac decompensation which invariably occurs in arteriovenous fistulae of long standing. As a matter of fact, the three main reasons for surgical intervention in cases of arteriovenous fistula are: (1) the prevention or cure of chronic venous insufficiency with its inevitable complications, varicose veins, eczema and ulceration, (2) the prevention or cure of cardiac decompensation, and (3) the prevention of excessive lengthening of the limb in patients where the epiphyses have not yet united.

Dry and Horton[2] have described spontaneous closure of a fistula. Non-surgical methods of treatment have met with uniform failure. Hines and Waugh[3] have reported a case of congestive cardiac failure due to a fistula.

Bleeding during dissection of the fistula was frequent and every small point was immediately coagulated to keep the field free from blood. This prolonged the operation to some extent but was a necessary procedure. There was no marked blood loss however and no blood transfusion had to be given either during or after the operation. The breaking down of the wound may be accounted for partly by the presence of syphilitic infection and partly by the damage to the wound edges caused by the application of the diathermy point close to the skin during the control of bleeding. The ultimate result was however very gratifying; the patient was markedly relieved and felt happy.

Out of the various surgical procedures available such as aneurysmorraphy, simple ligation and quadruple ligation with excision of the sac, the last one is the treatment of choice where it can be definitely ascertained that there is an adequate collateral circulation. The main danger in these cases is that of gangrene after operation due to the cutting off of the main arterial supply. It has been noted that even though actual gangrene may not develop after operation, symptoms of chronic vascular insufficiency such as pain while walking, coldness of the limb and early fatigue appear in the limb after a time.

The technique of ligature was modified to a certain extent in this case, using both tape and silk. It was feared that the broad tape acting as a foreign body, may prevent healing of the wound but this did not occur.

This case is particularly instructive as it illustrates the marvellous results of correct surgery when a clear cut indication exists. It also explodes the old bogey of not operating on a syphilitic patient with a positive serological test. The healing of the wound against all odds can only be attributed to that epochal discovery of Alexander Fleming —"Penicillin."

SUMMARY

A case of arteriovenous fistula was treated successfully by quadruple ligature and excision. The follow up for a year is recorded.

REFERENCES.

1. Cohen, S. M., and Schulenburg, C. A. R.: A case of arteriovenous aneurysm, Brit. J. Surg. **28**: 582-584, 1941.
2. Dry, T. J., and Horton, B. J.: Traumatic arteriovenous fistula involving the right femoral artery and vein: spontaneous closure, Arch. Surg. **33**: 248-252, 1936.
3. Hines, F. A., Jr. and Waugh, J. M.: Congestive heart failure; the result of arteriovenous fistula—report of a case, Proc. Staff Meet., Mayo Clinic **11**: 545-548, 1936.

MEDICINE

FOLLOW-UP STUDY OF ONE HUNDRED PRIVATE HYPERTENSIVE PATIENTS WITH CARDIOVASCULAR COMPLICATIONS, PAUL D. WHITE, E. GREY DIMOND & A. WILLIAMS.: J.A.M.A., **143** : 1311-1317, 1950. 5 references, 4 tables.

There have been a number of reviews of the effect of sympathectomy on the blood pressure in hypertension from public wards of general hospitals, but this one is from a select group of 50 patients followed up in private practice. These were followed up by one physician and were operated on by one surgeon between 1941 and 1946 and by one technique (lumbodorsal) and all seriously affected by the hypertension or by coronary disease or other vascular accidents. Patients with renal insufficiency were excluded.

For comparison, a control group also selected from private practice of one of the authors, was followed up for the same interval. In identical cardiovascular conditions but treated with somewhat restricted diets and sedatives. The duration of follow up for the living persons is from three to seven years. The detailed case history of these 50 cases have been given. Results can be summarised as follows :

The sympathectomised patients included 38 men and 12 women ; 8 of the 50 were between the ages of 30 and 40, 29 between 40 and 50 and 13 between 50 and 60. They showed a total of seventy-three complications : left ventricular weakness and failure in twenty-six ; cerebrovascular accidents in seventeen ; angina pectoris in twenty, and myocardial infarction in ten.

The 50 control cases included 37 men and 13 women ; 6 of the controls were between the ages of 30 and 40, 32 between 40 and 50 and 12 between 50 and 60. These had a total of sixty-one complications : left ventricular weakness and failure in twenty-three ; cerebrovascular accidents in nine ; angina pectoris in fourteen, and past myocardial infarction in fifteen.

After a three year follow-up of the 50 sympathectomized patients the result was excellent or good in 11 and fair with definite, though not decided, improvement in 11 ; in 5 instances there was little or no change ; 11 patients were worse, and 12 were dead. In contrast, among the controls, only 1 patient continued to be in good condition, 4 were in fair condition with some improvement, 4 were unchanged and 41 were worse or dead.

After the occurrence of the complications in the two groups the mortality in one year or less was 4 per cent. of the sympathectomized patients and 16 per cent of the controls ; in one to two years, 12 per cent of the sympathectomized and 32 per cent of the controls, and in two to three years, 16 per cent of the sympathectomized and 58 per cent of the controls. Thus, the sympathectomized hypertensive patients with serious cardiovascular complications showed by follow-up analysis, a considerably better status both in mortality and morbidity than did the non-sympathectomized persons. This is more impressive evidence of the beneficial effect of this therapeutic measure in certain cases than is the usual method of studying the effect on blood pressure alone in cases in which important complications do not exist.

The large number of failures still present a challenge, and this the authors are trying to meet, by the method of selection. A revised system of scoring for such selection has recently been introduced by Smithwick and would evidently have been helpful in excluding a considerable proportion of the cases herein reported in which unfavourable results were obtained in the sympathectomized patients.

J. C. PATEL.

INTRAVENOUS IRON IN THE TREATMENT OF HYPOCHROMIC ANAEMIA ASSOCIATED WITH RHEUMATOID ARTHRITIS, SINCLAIR, R.V.G., and DUTHIES, J. J. C.: B. M. J. 2: 1257-1258, 1950. 4 tables, 7 references.

The authors treated 51 cases of hypochromic anaemia associated with rheumatoid arthritis with intravenous iron. All these cases proved resistant to oral iron therapy. The intravenous iron used was 'ferrivenin' in the test dosage of 50 mg., followed by 200 mg. daily for 5 days and 'iviron', the test dose being 200 mg. followed by 400 mg. daily for two days. They obtained a satisfactory rise in haemoglobin levels in 38 cases and 13 remained refractory. Of the latter, 8 received a second course, but only two responded. There was a follow up in 23 cases for a period varying from 7 to 23 months, and the haemoglobin levels were maintained in 13 of these cases without further intravenous iron. In 3 of these cases a second course was resorted to, inspite of them responding initially to the treatment. The authors measured the absorption of iron in 7 cases and found it to be within normal limits. The cases responding to this regime of treatment evidenced a rapid fall in the erythrocyte sedimentation rate. In four patients, inspite of giving ascorbic acid 1 gm. intravenously on three successive days, the authors found no significant change in the E. S. R. or haemoglobin percentage. In rheumatoid arthritis there is a marked increase in the need of the tissues for iron and only when such need is met by large intravenous doses of iron, does iron become available for the formation of haemoglobin.

ERIC COELHO.

AMINOPTERIN IN THE TREATMENT OF ACUTE LEUKAEMIA, DACIE, J. V., MOLLIN D. L., DRSNER, E., AND WHITE, J. C.: B. M. J. 1: 1447-1457, 1950.

The authors report the results of treatment of 13 cases of acute and subacute leukaemia in children and adults with the folic acid antagonist, 4—aminopteroyl-glutamic acid (aminopterin). The dosage employed was 1 mg. daily for children and 1 to 3 mg. daily for adults until there was a pronounced haematological effect or toxic symptoms compelled its withdrawal. The drug was administered orally. In two of the six adults and in all of the seven children treated, clinical and haematological remissions were obtained. In the cases that showed response to treatment, the peripheral blood was rendered normal, or almost normal, for varying periods. There was also a clinical return to normality. Although the bone marrow picture improved strikingly, the leukaemic cells were never completely eradicated from them. All the cases that originally benefited by this regime, had a relapse and eventually died after becoming more or less refractory to treatment. As the toxic effects of aminopterin are serious and the difference between the therapeutic and the toxic dose is small, the action and results of aminopterin in any given case is unpredictable. Great caution is necessary in its use.

ERIC COELHO.

ALOPECIA AREATA: A CLINICAL STUDY, ANDERSON, I.: B. M. J. 2: 1250-1252, 1950.

This paper is based on a clinical study of 114 almost consecutive unselected cases. It was present in 2 per cent of the 15,000 new patients seen at Royal Infirmary, Sheffield. Out of the 114 cases, 81 were of simple alopecia areata, 24 extensive cases, and 9 of persistent areata. The sex incidence appeared to be equal in both. There was no relation to the colour of the hair. The disease occurred at all ages but was commoner in the younger age group. The disease typically begins as one patch, and may remain single or after a few weeks, secondary patches may appear on other parts of the scalp. In the author's series of cases there appeared to be a difference in the position of the primary patch between the two sexes,—male: 60 per cent occipital, 25 per cent fronto-vertical; and female: 27% occipital, 56% fronto-vertical. Recurrence was found in 32 cases (28 per cent.) There was a positive family history of alopecia areata in 22 cases (19 per cent.) and interestingly enough, 7 out of these 22 cases, had alopecia areata in their near relatives at the same time. The commonest precipitating cause was found to be mental shock or acute anxiety in 23 per cent of the cases. Focal sepsis does not play a big role in alopecia areata. In 27 per cent the health, both physical and mental, was excellent. Vitiligo was associated in 5 out of the 114 cases and nail changes were seen in 13 out of the 24 extensive cases of alopecia areata. The prognosis was graver in those cases when the disease occurred before 10 years of age, but was not much affected by other factors in the history. On the whole the prognosis is favourable, the permanent ill effects being less than 1 per cent. The aetiology of alopecia areata is still uncertain, the controversial point being restricted to whether it is a disease adaptation or of virus origin.

ERIC COELHO.

GAMMA GLOBULIN IN THE PREVENTION AND ATTENUATION OF MEASLES. CONTROLLED TRIALS IN DAY RESIDENTIAL NURSERIES. THE LANCET 2: 732-736, 1950. 9 tables, 7 refs.

Clinical trials were undertaken in 48 nursery schools of which 6 were residential. 457 children were given adult serum and 464 gamma globulin. The gamma globulin was prepared by a method described in the text. 250 mg. of protein contained 90-95% of gamma globulin. This was the usual dosage. In some, 500 mg. of protein was used. Controls were given 5 c.c. of adult serum. The contact children were inoculated within 72 hours of the appearance of the rash in the primary cases. Inoculated children were kept under observation for 21 days and those in day nurseries were visited in their own homes during this period if they were absent from the nursery. The following conclusions were reached:

In a series of controlled trials in day nurseries, gamma globulin was given in 225-450 mg. doses to 212 susceptible measles contacts between the ages of 6 months and 5 years; 31.6% developed measles and 94% of these showed excellent or satisfactory modification. Adult serum was given in 5 ml. doses to 215 contacts of similar age and exposure; 57.2% developed measles, and 48.9% of these showed none (or doubtful) evidence of modification. The attack-rates for children receiving 225-300 mg. and 450 mg. of gamma globulin were 33.7% and 21.6% respectively; whereas in the corresponding groups of children receiving 5 ml. of adult serum the rates were 55.4% and 65.8%. The duration of passive immunity depended on dosage; with the larger dose some protection for periods up to six weeks was observed. Recommendations are made on the dose of gamma globulin to be given to exposed children at different ages to modify or prevent an expected attack of measles. Reactions to the prophylactic injections in this trial were minimal and unimportant. No serious complications were observed in the globulin group.

J. C. PATEL.

ANTIBIOTIC SYNERGISM AND ANTAGONISM. ANNOTATION B. M. J. **11** : 1160, 1950.

Two or more chemotherapeutic agents have been recognised to be more effective than one and probably in a smaller dosage. Penicillin and sulphonamides combined were used and are effective against *S. typhi in vitrio.* Para aminosalicylic acid and streptomycin together are more effective than either one against pulmonary tuberculosis. The combination of two agents may have an opposing effect also. There is mutual interference by some chemotherapeutic agents. Penicillin alone has a partial bactericidal effect on enterococci (*Str. faecales*) which is accelerated by the addition of streptomycin in a concentration which, acting alone, has little effect, but the bactericidal effect is diminished by adding chloramphenicol to penicillin. This combined effect is evident in endocarditis when penicillin alone will not have a complete action. Antagonism between penicillin and chloramphenicol has been shown in experimental animals like mice incoulated with *Str. pyogenes* by a higher mortality when the dose of chloramphenicol was higher. This may be dangerous in 'shot gun' antibiotic therapy. The explanation offered is that penicillin and streptomycin act as bactericidal antibiotics, while the newer ones (aureomycin and chloramphenicol) are bacteriostatic. Penicillin acts as a bactericidal agent only to multiplying bacteria and, if other antibiotics stop this process, penicillin has no action. One has to bear in mind while combining anti biotics that the newer two antibiotics might interfere with the action of either of the older ones.

J. C. PATEL.

SURGERY

COLOSTOMY, EWING, M. R.: Postgraduate Med. J. **26** : 584-589, 1950.

Many surgeons believe that a colostomy leaves the almost insufferable burden of a permanent incontinent abdominal anus and hence try to advise a sphincter-saving operation. The author gives the view point of 20 old colostomy patients in their own homes, as given to a hospital almoner. The youngest patient was 42 and the oldest 79. The younger and more intelligent the patient, the less trouble he has with his colostomy. The higher the social status, the easier was his lot. One patient was able to enter the bright social life of her 18 year old daughter from whom she had so far been able to keep the secret of her disability. In their standard of personal cleanliness and hygiene, they were able to have the amenities of a social life without the slightest trace of faecal odour, but in poorer homes with a small bathroom or in boarding houses, life was slightly uncomfortable. Some were able to get their full employment, but a number of patients who came in for colostomy and had retired, led a life of leisure, pottering about the house, doing odd jobs in their gardens and seeking the comforts of their pipe on the bench park. Only two were bed ridden patients, one was 79 and the other had some other illness incapacitating her. Some complained bitterly about the restrictions in the diet which their colostomy made necessary. Their diet symptoms became monotonous to avoid recurring diarrhoea. Another disadvantage was experienced on the dressings, the habit of using large amount of dressing came from the hospital. Tolerance of alcohol was good and they could safely take their customary evening glass o ale. Some of them had complications like prolapse, hernia, skin stenosis, bleeding polypi and intestinal obstruction. It was concluded that the lot of the average colostomy patient is by no means an unhappy one and that an alternative operative procedure which attempts to spare him this disability must not be allowed in any way to diminish his chances of continual survival.

J. C. PATEL.

PEDIATRICS

LESSONS FOR FUTURE TREATMENT FROM 472 FATALITIES IN DIABETIC CHILDREN, JOSLIN, E. P., AND WILSON, J. L.: B. M. J. 2,: 1293-1296, 1950.

The authors have tabulated and compared the causes of deaths of children suffering from diabetes in the pre-insulin and the insulin eras. They were encouraged to learn that the average duration of diabetes in the 135 children who succumbed in 1944-1949 exceeded the average duration in those dying in the previous six-year period, 1937-1943 by approximately eight years, and that they were eight years older when they died. In tabulating the causes of death in 135 diabetic children during the period 1944-1949, the whole picture has completely changed. The incidences of death due to diabetic coma has steadily dropped from 86 per cent in the pre-insulin era to 9.6 per cent since 1944, while the frequency of cardio-renal vascular disease has steadily risen from 0.6 per cent to 56.3 per cent. In the cardio-renal vascular group, only two cases of renal disease were recorded prior to 1937, but recently the figure has risen to 37 per cent. Prior to 1937, no cases of angina pectoris or coronary disease appeared, but since that time the percentage varied from 2.5 per cent to 10.4 per cent. Apoplexy was observed only once among these children before 1944 and in only three cases since that time. Fatal infection rose from an incidence of 6.4 per cent before insulin to a peak of 24.7 per cent in 1937-1943, but since the reintroduction of specific chemotherapeutic agents and antibiotics they have fallen to 7.4 per cent. From the statistics of 135 deaths of diabetic children within the last 6 years,—11.2 per cent dying from tuberculosis, 5.19 per cent from renal disease and 8.8 per cent from diabetic coma, the authors concluded that diabetes in childhood should be followed more closely and only then can needless death be avoided. Continuity of treatment is very essential. Roentgenograms of the chest should be taken yearly and a constant watch kept over the kidney functions. Furthermore in order to preserve the diabetic children in comfort and to prolong their lives, it is of paramount importance for inexpensive and attractive opportunities, in children's and adolescents' camp and especially in hospitals, of reviewing their physical condition and promoting morale and zeal for the continuing control of their diabetes.

ERIC COELHO.

PAROXYSMAL SUPRAVENTRICULAR TACHYCARDIA IN INFANTS, BROWNLEE, W. M., WATERS, E. M., MCCLENDON, S. J. : Am. J. Dis. Child. **79** : 838-845, 1950.

The picture in infants is different and much more serious than in adults. If tachycardia continues, congestive failure develops. In the typical cases, there is vomiting. The baby becomes limp, gray and prostrated. The heart rate is rapid and difficult to determine, usually about 220 to 300. The heart enlarges, becomes greatly dilated, and if this persists congestive failure rapidly sets in. There are severe dyspnoea, enlargement of the liver and spleen, abdominal distension, sometimes elevation of temperature to 102° F. and leukocytosis. The roentgenogram of the chest shows cardiac enlargement and pulmonary congestion. The attack may stop spontaneously or end fatally if proper treatment is not given. When tachycardia stops, all symptoms promptly subside.

Various methods of treatment have been recommended, but are usually ineffective in infants. Among those used are, pressure on the carotid sinuses and on the eyeballs, induction of vomiting, administration of digitalis, quinidine, 20 to 25 per cent magnesium sulphate intravenously, neo-synephrine, and lanatocide C. Two drugs found effective in infants are acetylcholine bromide and acetyl-beta-methylcholine (mecholyl). Acetylcholine must be given intravenously to be effective. Mecholyl can be given subcutaneously. This is significant when the routes of administration in infants are considered, the subcutaneous route being much easier. The side actions of mecholyl are much more than those of acetylcholine, and include flushing, a feeling of warmth and then of cold, sweating, salivation, lacrimation, and palpitation. These side actions are temporary, and a small price to pay. The usual dose is 1 mg. to 40 mg. depending on the infant's age. Wright administered 100 mg. accidently without any bad effect.

The authors report a case of supraventricular tachycardia in an infant 10 weeks old, probably the youngest case reported so far. 1 mg. of mecholyl brought the heart rate from 350 to 150, and then to 70 after a second dose was given. The child was later put on tinct. digitalis 10 drops daily with excellent results. The authors recommend the use of mecholyl in the treatment of supraventricular tachycardia and digitalis prophylactically for 3 months or longer following an attack.

F. A. NAZARETH.

SITUS INVERSUS, BRONCHIECTASIS AND SINUSITIS, BERGSTROM, W. H., COOK C.D., SCANNEL, J. AND BERENBERG, W.: Pediatrics 6: 573-580 1950.

Kartagener in 1933 described a triad consisting of bronchiectasis, situs inversus and sinusitis. He advanced a hypothesis that hereditary predisposition may be a determining factor in certain cases of bronchiectasis. Statistics have shown that certain persons with situs inversus may have a genetic predisposition to bronchiectasis. Situs inversus occurs in approximately one in 8000 persons; bronchiectasis is found in from 12 to 23 per cent of persons with situs inversus, but in only 0.3 to 0.5 per cent of the general hospital and clinical population. The possibility that the position of the great vessels in cases of dextrocardia may interfere with normal bronchial drainage and thus cause bronchiectasis remains to be proved; stillborn or newborn infants with dextrocardia do not show pathological changes of bronchiectasis. Kartagener's syndrome is a pediatric problem; approximately 90 per cent of the cases reported show the onset of symptoms at 14 years or under.

The authors report a family of 6 children, 4 of whom had sinusitis and clinical bronchiectasis of the acquired type with symptoms beginning in early childhood. The parents, except for chronic sinusitis in the father, were normal. 2 of the 4 affected children had complete situs inversus as well and also two other additional anomalies: in one, hypospadias; in the other, congenital heart disease with cyanosis. The other two children had bronchiectasis requiring lobectomy. Two other siblings were quite healthy.

F. A. NAZARETH.

ERRATA.

Vol. 5, January 1951, page 21, under abstract "Present Status of the Treatment of Syphilis," read J. K. Mehta as T. K. Mehta,

Vol. 5, January 1951, page 30, under abstract "Sialography in Diagnosis" read E. J. Borges as Eustace de Souza.

BOOK REVIEW

LOOSE LEAF MODERN MEDICAL TREATMENT. GUJRAL. M.L. M.B., M.R.C.P. (Pp. 468. Rs. 25). published by the author 1950.

The Indian medical profession will have to write, sooner or later, text books for their students. The beginning has been made by some in all parts of India. These books like Ghosh's Materia Medica are admirable and are popular with students throughout the whole of India. 'Loose Leaf Modern Medical Treatment' by Dr. Gujral was published in 1949. He has just added a replacement supplement of 1950. The book is divided into two parts. Part one deals with general principles of treatment. This is dealt with in a separate manner which, so far, very few books on therapeutics have treated the subject. The Indian medical student is apt to remember by heart the details of treatment without understanding the basic principles which govern the therapeutics of a disease. Dr. Gujral, by dealing with this aspect of treatment separately at the beginning of the book has done a great service to medical students and the practitioner. The systematic treatment given in the second part has been dealt with in short sentences in a positive manner which rarely leaves a doubt in the mind of the reader. The drugs of doubtful value are either omitted or decried. At the end of the book there are nine appendices. Each one of these is most useful, to a student going up for an examination or to a busy practitioner, for the volume of the valuable ready information contained in them, and that part alone is worth the price of the book which is a moderate one. It is nicely bound and printed. The loose leaf character of the book with replacement supplements will help to keep the book abreast of new developments. Dr. Gujral is well qualified to write a book on medical treatment as he is the Professor of Pharmacology at the Lucknow University and physician to the teaching hospital. The book is worth keeping on the table for a busy practitioner for ready reference and for the final year medical student.

J. C. PATEL.

ALL INDIA CONFERENCE ON DERMATOLOGY AND VENEREOLOGY.

An All-India Conference on dermatology and venereology will be held at Calcutta on Saturday, the 14th April and Sunday, the 15th April 1951 under the presidency of Dr. A. C. Rebello of Bombay. It is organised by the Association of Dermatologists and Venereologists of Bengal with the co-operation of the Associations of Dermatologists & Venereologists of Madras and Bombay.

NOTICE TO CONTRIBUTORS

The Indian Journal of Medical Sciences which appears monthly, publishes original articles in all branches of medicine and allied sciences, case reports, progress reviews, book reviews, summary of current medical literature and author's summaries. Papers submitted for publication and all editorial communications should be addressed to the Editor, Indian Journal of Medical Sciences, Back Bay View, New Queen's Road, Bombay 4.

Papers submitted for the Journal are accepted on the understanding that they have not been and will not be published in whole or in part in any other journal; they are subject to editorial revision.

Manuscripts should be in double-spaced typing on one side on quarto or foolscap sheets, with a margin of not less than 2 inches. They should bear the name and full address of the author to whom proofs are to be sent. A paper should conclude with a brief summary giving in numbered paragraphs the results and conclusions described in the paper; it should not exceed 1/20th of the length of the paper.

Tables.—Tables should be typed on separate numbered sheets and referred to the text by Arabic numerals.

Illustrations.—Illustrations will not be accepted unless they reach a certain standard of excellence technically, present an attractive appearance and add significantly to the value of the presentation. They are to be referred to in the text by Roman numerals. Legends or captions are to be typed on separate sheets and numbered correspondingly. Line drawings and graphs, which should be about twice their intended final size, are to be carefully drawn in Indian ink on tracing linen, or card board, or stout smooth white paper; blue-lined graph paper of good quality may be used for graphs. Lettering of drawings and graphs must be lightly written in pencil. When half-tone reproduction of X-ray or other illustrations is required the author is advised to send the original film unless he wishes to bring out special points in a print of his own choice. Photographs and photo-micrographs should be printed on glossy paper, should be larger than the size desired for reproduction, and if transmitted through the post in a tube, should be rolled with the picture outside.

References.—At the end of the paper references should be arranged in the alphabetical order of the author's names and should include: author's name, followed by initials; the name of the article, name of journal, volume underlined; pages, and the year. References made to books should include the author's name followed by the title underlined, pages, town of origin, the publisher and the year.

Examples. 1. Coller, F. A., and Maddock, W. G.; The Function of Peripheral Vasoconstriction, Ann. Surg. **100** : 983-992, 1934.

2. White, J. C., and Smithwick, R. H.: The Autonomic Nervous System, pp. 271, New York, the Macmillian Company, 1941.

Citations in the text should be by the author's name followed by the number listed in the reference.

Proofs.—Contributors will receive one proof in galley, but it will be assumed that all but verbal corrections have been made in the original manuscript.

Reprints.—25 reprints of an article will be given to the author or divided among the authors. Additional reprints can be supplied at cost price if application is made when the proofs are returned.

Copyright.—Papers which have been published become the property of the Journal and permission to republish must be obtained from the Editor.

Indian Journal of Medical Sciences
(INCORPORATING THE MEDICAL BULLETIN)

VOLUME 5 APRIL 1951 NUMBER 4

COPYRIGHT BY THE INDIAN JOURNAL OF MEDICAL SCIENCES

THE PROBLEM OF RHEUMATISM AND UNITARY CONCEPTION AND CONTROL BY MODERN METHODS §

M. G. Good*

I propose to deal with the Problem of Rheumatism under two main headings, viz., I. Non-articular or Common Rheumatism, and II. Articular forms. In contrast to the present trend to describe more and more forms and syndromes of the rheumatic disease—more than 200 forms have already been described (P. S. Hench, 1949),[3] I shall try to advance a **unitary conception** of that widespread malady.

OBJECTIVE DIAGNOSIS OF PAIN

In approaching the problem one has to realise that rheumatism is the prototype of a great number of maladies the cardinal symptom of which is **Pain—maladie de la douleur** (Leriche). It is true that it is frequently associated with disturbances of movements and|or locomotion; but these complaints are due solely to pain. If we are able to relieve the pain—e.g. temporarily by cortisone—the patient appears almost normal in every respect. Unfortunately pain is a purely **subjective** phenomenon. It varies a great deal from slight discomfort and tiredness to the highest degree of almost unbearable suffering, rarely associated with a feeling of anguish. In addition, sensitiveness to pain appears to vary very much in different individuals; they may be hypersensitive, normosensitive or hyposensitive to pain, probably owing to an individually differing threshold of pain. That such a subjective phenomenon does not satisfy the requirements of a scientific diagnosis becomes apparent by a comparison with "fever": the exact diagnosis can by no means be based on the sensation of the patient who may feel hot, nor on the sensation of the examiner, but requires the objective finding of a thermometer.

---

§Paper read at the 1st International Congress of Internal Medicine. (Paris, 11-14 Sept. 1950). The technique of Diagnosis and treatment was demonstrated at the Beaujon Hospital, Paris-Clichy (Prof. R. Fauvert).

*London, N. W. II.

The study of objective criteria of pain on many hundreds of patients has led to a most remarkable finding: in rheumatism as well as in some other, especially functional maladies, the pain complained of is of **muscular** origin. It arises from anatomically defined muscular areas, called "myalgic spots."

Definition of myalgic spots: small muscular areas localised in the origin, insertion, border or course of a muscle or its continuation,—the ligaments—which cause referred pain, and on pressure elicits a reflex-like jerking in any part of the body and|or a grimace.

RHEUMATIC MYOPATHY (MYALGIA) AS THE BASIS OF NON-ARTICULAR RHEUMATISM

Definition: a muscular disease, most likely of a functional nature, characterised by "myalgic spots" which give rise to the triad: referred pain of a dermatome-like delineation, temporary weakness and loss of power in the affected muscle, and neuralgiform symptoms (paraesthesia etc.)

It is to be noted that the myalgic spot is the fixed pole in the ever changing phenomena of rheumatism, and the condition **sine qua non** for the diagnosis. Sore spots or trigger points, mostly referred to in the literature, are neither indicative nor the real root of rheumatic myalgia.

PAIN PHENOMENA IN RHEUMATISM

They consist of two types, viz. 1. a deeply felt pain of a more or less agonizing or annoying character, often called "ache" by patients, which more often than not can be properly localised by the sufferer, and 2. a superficial kind which can be approximately delineated. From the point of view of practical diagnostics the fact is very significant that the pain is elicited and|or aggravated by contraction, and diminished by relaxation of the affected muscle or muscles.

RULE OF DERMATOMES

The examination of more than a thousand patients has established the fact that the relation between the areas of pain mapped out by patients themselves and the individual muscle or muscles responsible for, or causing them, is determined by the rule of dermatomes: pain is referred to skin areas, approximately dermatome-like in delineation, which are mostly supplied by spinal nerves (roots) innervating the muscles causing it. For anatomical reasons pain may also be referred to dermatomes which are the direct neighbours of the main root.

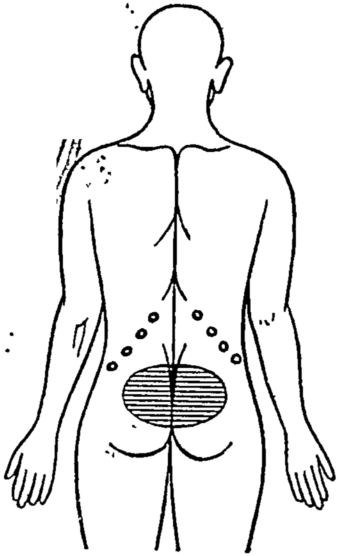


Diagram 1.
Lumbago.

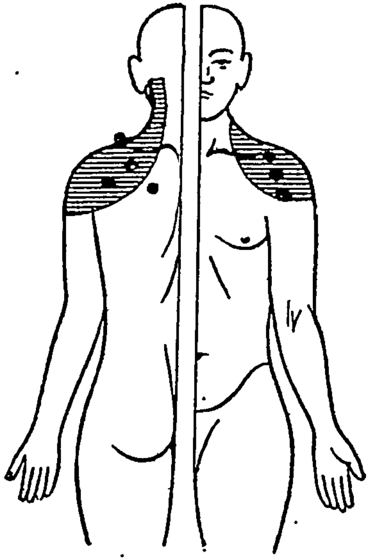


Diagram 2.
Pain-shoulder.

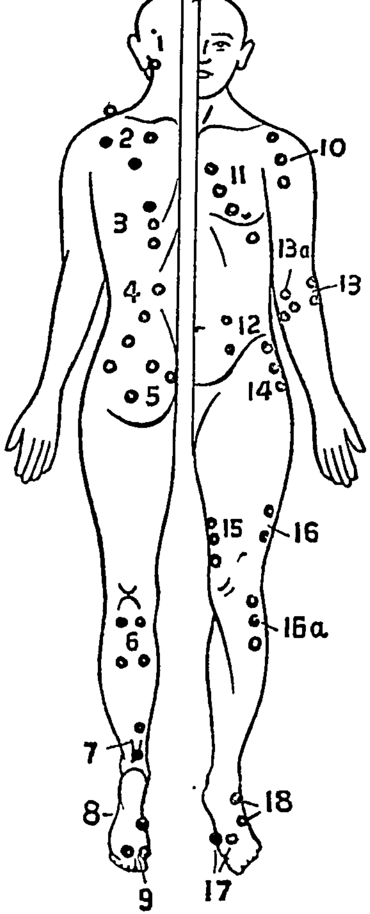
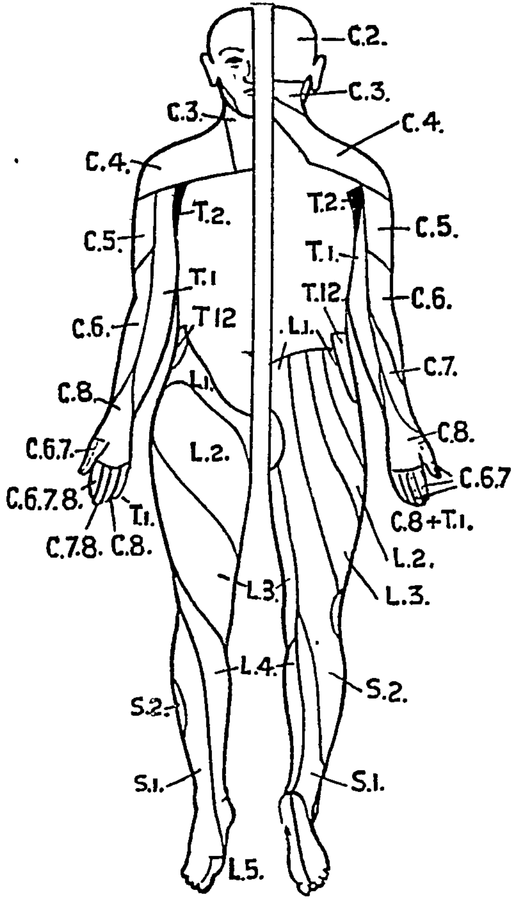


Diagram 3.
Distribution of MS in different parts of the body.



Diagrom 4.
Cutaneous areas-dermatones innervated by the different spinal nerves.

1. M. sternocleidomastodieus.
2. M. trapezius.
3. M. sacrospinalis.
4. M. quadratus lumborum.
5. Mm. glutei.
6. Mm. gastrocnemii.
7. Tendo Achilles.
8. M. Tibialis post.
9. Mm. flexor ae abductor obliquus hal.
10. Tendo M. bicipitis.
11. M. pectoralis maj.
12. M. rectus abdominis.
13. Mm. extensores manu.
13a. Mm. flexores manu.
14. M. tensor fasciae latae.

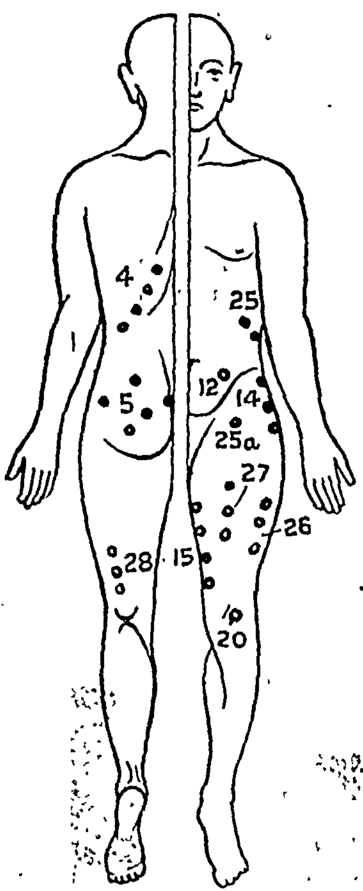


Diagram 5.
Arthritis of hip.

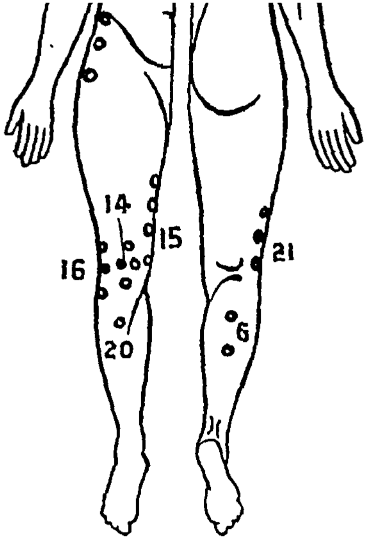


Diagram 6.
Arthritis of knee.

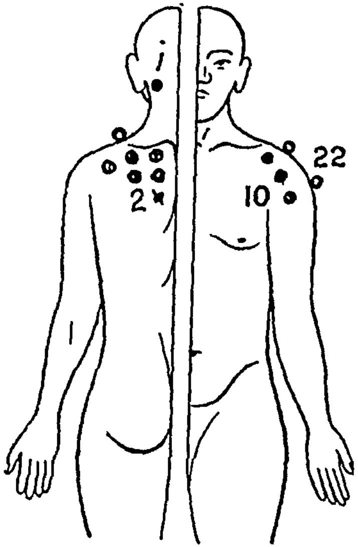


Diagram 7.
Arthritis of shoulder.

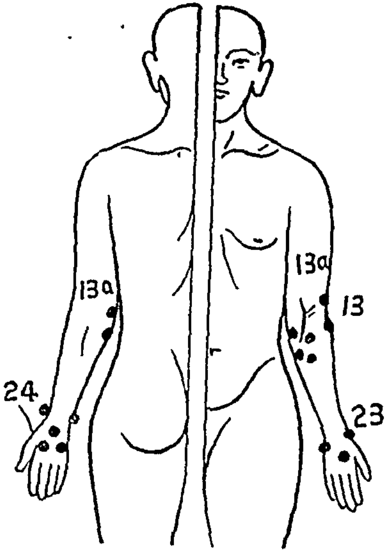


Diagram 8.
Arthritis of wrist.

15. M. semimembranosus-tendinosus.
16. M. vastus lateralis.
16a. Mm. perinei.
17. M. extensor hal. brev.
18. M. interosseus dorsalis.
19. Lig. patellare.
20. Pes anserinus.
21. M. biceps femoris, lig. collaterale fibulare.
22. M. deltoideus.
23. Mm. flexores carpi radialis, ulnaris, palmaris longus.
24. Mm. extensores carpi rad, long, ulnaris, palmaris long.
25. M. obliq. abd.
25a. M. ileopsoas.
26. M. rectus femoris.
27. M. adductor magn.
28. M. biceps femoris.

TECHNIQUE OF LOCATING MYALGIC SPOTS

1. The patient is asked to map out on a chart (diagram), front and back, the painful skin areas as exactly as possible, from which he suffers at present, as well those he felt in the last three months. After some experience one learns soon to correlate these areas of pain to the responsible myalgic areas localised in muscles innervated by the same spinal nerves. Actually the painful skin areas are in shape and distribution mostly very characteristic, and recur with almost monotonous regularity, e.g., in lumbago, patients delineate an oval or circular symmetrical area in the lower part of the back (Diagram 1); in shoulder pain, a skin area corresponding to C 4-5. (Diagram 2).

2. In my experience the best clue is given by finding out on questioning the patient or by passive movements, which movement brings on, or aggravates the pain. In this way one is led to examine especially thoroughly the muscle or muscle group taking part in a pain producing contraction.

3. By light touch one palpates with the finger tips the suspected muscle; often one feels in its course small areas harder to the feel than the surrounding. On these and its origin, insertion or course one exercises a hard pressure or pressure only. The presence of a myalgic spot must be diagnosed only, if the patient shows, as mentioned above, a reflex-like jerk, or cuts a face. This sign is pathognomonic and most reliable. It is of the utmost importance to distinguish the objectively located myalgic spot from "sore spots" or "trigger points", the localisation of which depends on the subjective sensation of the patient. Unfortunately the literature contains incorrect or no descriptions of myalgic spots, leading to great confusion. In spite of my repeated stress laid on the objective character of the latter, it is often or even mostly said to be identical with trigger points or nodules. Actually the latter are of no diagnostic significance, being in most cases conspicuous by their absence. The confusion seems to have arisen from the fact that a myalgic spot is often harder to the feel than the surrounding tissue, because the diseased area is in a state of tonic (spastic) contraction. In parenthesis I mention here that the muscle spasm disappears within 30—50 seconds, on the appropriate injection of procaine.

DYNAMIC PATHOLOGY

There is consensus of opinion that with the methods available at present no histological changes are ascertainable. This fact, however, does not justify the conclusion that non-articular rheumatism because it has no pathology is an "imaginary" or psychogenic malady. On the other hand the theory, propounded in 1938 by the writer, that the disease consists in a disturbed circulation—diminished blood flow leading to a relative hypoxia—mostly by vasoconstriction in the myalgic areas, appears best to account for the traid, pain, disturbed muscular function and paraesthesia. The functional pathological condition may be brought about by many "causes"; infections, toxic conditions, allergy, autonomic imbalance, affecting the local capillary tonus (blood flow), psychological factors like mental strain, long continued worries, and trauma. An injury, mostly of an indirect nature, is in my experience a most frequent factor, possibly in the form of a "microtrauma", escaping the memory of the patient, to which the malady can be traced: among five hundred cases studied in the British Army during the last War about twenty to thirty per cent could with certainty be traced to a recent or previous injury—traumatic myalgia. One has also to keep in mind the great significance of the K:Ca ratio, which is intimately connected with the function of both divisions of the autonomic nervous system and hence influence, like some hormones—adrenalin, acetylcholin—, metabolites (histamin, adenylphosphoric acid, lactic acid), endocrines, the local capillary tonus, blood flow and oxygen supply.

The localisation of the commonest myalgic spots in the different parts of the body is shown in Diagram 3.

THERAPY

The most efficacious treatment consists in injection of a small quantity—1-2 ml of a 2 per cent solution of procaine intramuscularly and accurately into each myalgic spot. The therapeutic results are most gratifying, spectacular and often marvellous. Few things in clinical medicine could be more dramatic than the rapid relief obtained, e.g. in a case of acute lumbago by the injection of 5-10 ml of procaine into the borders of both quadrati lumborum. In my extensive experience the treatment leads to a rapid relief of pain and restoration of function of the diseased muscles in a short time. The beneficial and permanent therapeutic results could not easily be equalled or surpassed by any other method available at present. Among British Rheumatologists, Warren Crow (1949)[1] is the first to confirm the extreme importance of the myalgic spot (MS), and the injection of procaine "is most valuable of all weapons for the treatment of the individual rheumatic".

ARTICULAR RHEUMATISM

The thorough study of rheumatic, traumatic and idiopathic myalgias in the last 15 years resulted in a very unexpected and surprising finding, viz., that rheumatoid as well as osteo-arthritis are very frequently associated with objectively ascertainable myalgic areas in the neighbouring muscles of the affected joints. What is even more amazing is the observation that the myalgic spots found in cases of arthritis were partly, or sometimes to a large extent, Identical with those characteristic of non-articular rheumatism. These recurrent observations led me to put forward as a working hypothesis a daring, and, if you like, revolutionary conception: arthritis, rheumatoid or otherwise, is primarily a muscular disease, viz. a **Peri- and Para-Articular Myopathy, which leads secondarily** to the well known morbid changes in bones, synovial membranes and other joint structures. Obviously it was incumbent upon me to subject the hypothesis contradicting the unanimous opinion of rheumatologists and even the term arthritis, sacred through centuries-old use, to a most rigorous and searching scientific test. This has been done on a great number of cases: in the last two years about a hundred and twenty cases, mostly rheumatoid arthritis, were thoroughly investigated, with the surprising result that myalgic spots in muscles, tendons and ligaments of the diseased joints could be ascertained, in every case, by objective criteria, which are specific and characteristic for every individual joint. As an illustration may serve Diagrams 5-8, showing the typical myalgic areas in arthritis of the hip, knee, shoulder and wrist respectively. A most remarkable finding is that the myalgic spots are practically the same in rheumatoid (atrophic), in osteo-arthritis (hypertrophic) and in traumatic arthritis. This result makes it appear very likely that the conception of a peri-and para-articular myopathy is of a **General** nature, applicable to any form of arthritis, e.g. infective, toxic and others. If this theory be correct the designation **Myo-Arthropathy** or **Myopathic Arthritis** of rheumatoid, osteitic and traumatic types would appear to be appropriate.

The discovery of specific myalgic areas, objectively ascertainable in arthritis obviously opened a new avenue to a rational and promising therapy. Procaine injection of the myalgic spots appeared the method of choice, as in non-articular rheumatism. Regarding the technique I should like to mention that the two per cent solution was injected only intramuscularly, into the tendons and ligaments, avoiding the subcutaneous structures and never into the joint (intra-articularly).

RESULTS OF PROCAINE THERAPY

Of the hundred and twenty cases examined during the last two years, I had the opportunity of applying the procaine treatment in eighty patients. The results obtained show definitely that the method gives very satisfactory and most gratifying therapeutic successes, practically in every case treated. It has proved possible to control pain, permanently, in a spectacular way. In not far advanced stages of the disease, without severe and gross roentgenographic changes, the affected joint can be restored to a normal range of movements. But even in cases of many years' standing, upto twenty years, with severely damaged and wasted muscles it has proved feasible to restore the function and range of movement—without pain (!)—to a large extent. It appears unbelievable, but is none the less a true fact that joints which have been fixed for years, not the slightest movement being possible, actively or passively, so that they appeared ankylosed to the expert, can be made to move again to a certain extent, enabling the patient to use the formerly crippled joint sufficiently for many practical purposes. I report a fact that among my cases are a number of patients treated up to two years ago, without a recurrence of pain or other complaints in the joints treated. It may not appear superfluous to emphasize that no **Intra-Articular** injection was ever made, but only the **objectively** located myalgic areas treated. As a rule, every spot need be injected only once. Exceptionally, especially if the area was not thoroughly and accurately treated, a second injection may be necessary to obtain a total relief. In the early stages of the disease the results are often dramatic and spectacular: it is possible to relieve pain fully and restore the full range of movement in the early stage of arthritis genu by three to four treatments. Since the relief is apparently permanent, it appears to the patient like the work of a magic wand. It is noteworthy that the oedematous swelling often present in arthritis slowly disappears, so that the diseased joints soon regain their normal contours, e.g., in wrist, knuckles, knee and ankles. Often the treatment is accompanied by a remarkable loss of weight, probably due to the excretion of fluid accumulated in the peri-articular and subcutaneous tissue spaces. Another result of the therapy is worth stressing, viz., the very great improvement in general health, and a considerably improved mood. Patients who have been in pain and incapacitated for years look extremely depressed, with dull eyes, extremely self-centred, not in the least interested in anything but the enumeration of their unceasing complaints. After a few weeks' treatment they look much different, their eyes are clear, they look straight; they are more cheerful and start taking an interest again in their surroundings and fellow creatures.

Physicians rarely think of the fact that the skeletal muscles, the source of all human and animal physical power institute the largest organ of the body, contain about one third of the total blood, and are subject to great wear and tear during waking hours. It is therefore hardly surprising that recent research has proved, I think conclusively, that the musculature plays a very frequent and significant role in the pathogenesis of many, especially functional maladies, and also in Rheumatic Disease. Looking at it retrospectively, it appears probable that the outstanding importance of the skeletal muscles for pathology and medicine was in the past not sufficiently appreciated, because of the lack of objective criteria of the rheumatic and idiopathic myopathy, which is often of a functional nature. Its main pathogenetic mechanism is most likely **Hypoxia** in the myalgic areas, brought about by a blood flow **relatively** deficient in relation to the momentary function of the contracting muscle. It is well known (Sir T. Lewis, 1938)[4] that a muscle made to contract under ischaemia, i.e., total lack of oxygen or **Anoxia**, causes severe agonizing pains, and is very soon paralysed. It is reasonable to assume that many causes, e.g., trauma, infections, toxic conditions, allergy, climatic changes, especially of a sudden nature, an imbalance of the autonomic nervous system, emotional strain by acting on the local capillary tonus may lead to the same **functional pathology** in the myalgic areas. Only after such a morbid condition has been going on for a longer period—e.g. frequent vasospasms of long duration—histo-pathological changes of a secondary nature may develop in joint structures, the muscles themselves, Heberden nodules and related anomalies in the subcutaneous tissues.

Leaving at present rheumatic fever out of the picture, we thus arrive at a **unitary conception of the rheumatic disease.** Instead of hundreds of syndromes, lately indulged in by some writers, we claim that fundamentally there exists one disease only, a rheumatic myopathy, or myalgia simplex responsible for non-articular rheumatism, which is as well the primary pathology of the articular forms. The latter are essentially a peri-and para-articular myopathy, which, owing to the severity and long duration of impaired blood supply, probably aided and aggravated by many other conditions, like imbalance of endocrines, emotional strain and other psychological factors, leads **secondarily** to histological changes in muscle, tendon and bony structures.

The unitary conception of the Rheumatic Disease appears to be in full harmony with the remarkable and most gratifying therapeutic results of the **local** procaine therapy, which, I contend, cannot be easily equalled or surpassed by any other method known at present, cortisone or otherwise.

The claim appears to be justified that the modern methods of diagnosis and treatment enable us to control Rheumatism, including the articular forms satisfactorily. In face of great doubts likely to be expected, I'll be glad to demonstrate the technique at the Beaujon Hospital (Prof. R. Fauvert).

The myogenic theory of arthritis is, as mentioned above, of a general nature, applicable to any form of arthritis. Many rheumatologists possibly will be reluctant to accept so audacious a concept. Physicians, in general, are usually rather chary of theories. Some workers tell us even that a general theory, being mere words, has no justification in scientific medicine. But I feel that Medicine may profit a great deal by following the lead of her older sisters, physics and chemistry, the uncomparable advances of which are to a large extent due to the greatest simplification of concepts and definitions. Natural scientisst are not averse to a conception beyond our imagination, as long as it allows a greater simplification of the Laws of Nature. I refer specially to the General Relativity Theory. Its greatness and ingenuity is, as I see it, due to the fact that instead of many axioms required in Euclidean geometry, Einstein makes use only of one axiom, the distance between two points is defined by the equation:

$$S\int ds = S\int \sqrt{\Sigma g_{\mu\nu} dx_{\mu} dx_{\nu}} = 0. \quad ; \mu\nu = 1, 2, 3, 4.$$

The formula, the variation of an integral, requires for its understanding the knowledge of higher mathematics, especially the differential and tensor calculi. But even to a non-mathematician it is fairly obvious that Einstein's basic axiom implies a four dimensional continuum or space for its geometry. But inspite of the fact that a 4-dimensional space contradicts our experience of the space we have been familiar with, and in addition even surpasses our imagination, physicists have accepted the theory which, for weal or woe, has opened the Atomic Age.

By contrast the myogenic theory of arthritis contains nothing which contradicts our present medical experiences. Since the conclusions drawn from the myogenic theory have led to a great therapeutic advance, I feel that medical research workers might be encouraged to follow the lead of physics and chemistry in making more often use of a general theory, as a more perfect scientific tool, which may enhance the progress of Medicine.

Modern scientific research has given doctors the power to deal with the problem of Rheumatism in a very effective and satisfactory way. I shall be glad and much rewarded for 15 years' labours, if the method could be taken up wholeheartedly by the medical profession at large. May I appeal to you to make the widest use of that power for the great benefit of the innumerable rheumatic sufferers of your countries, and to your own greatest satisfaction. May I appeal to you to join forces under the motto: *La mort au rhumatisme.*

REFERENCES

1. Crow, Warren H.: Rheumatism, 2nd ed. p. 154. London, 1949.
2. Good, M. G. Diagnosis & treatment of muscular rheumatism, Brit. J. Phys. Med 1: 302, 1938.
   Idiopathic Myalgia, simulating visceral and other diseases, Lancet, 2: 326, 1940.
   Rheumatic Myalgias. Practioner, 146: 167, 1941.
   Traumatic Myalgias, ibid. 148: 236, 1942.
   500 cases of Myalgia in the British Army. Ann. Rheum. Dis. 3: 194, 1942.
   Muscular sciatica. Clin. Journ. 72: 66, 1943.
   Diagnosis and treatment of Low Backache. Med. Press, 8. Dec. 1948.
   New approach to and conception of rheumatoid arthritis. Remarkable therapeutic results. Preliminary report. London privately printed). March, 1949.
   Objektive Diagnose des Muskel—und Gelenkrheumatismus und seine Behandlung. Kongr. Ber. Deut. Inn. Med. 55: 84, 1949.
   Modern conception of non-articular rheumatism Acta Med. Orient. 8: No. 3-4, 1949.
   What is Fibrositis? "Rheumatism", October, 1949.
   Conception nouvelle et traitement de l'arthrite rhumatoide, Paris Medical, No. 41, 1949.
   Acroparesthesie—myalgie idiopathique du coude, ibid. No. 42. 1949.
   A general theory of pain. Zschr. Rheumaf. 8: Sept. 1949.
   Rheumatoid arthritis. Extraordinary therapeutic results by procaine injections of specific myalgic spots. ibid: 9: 1—2, 1950.
   Objective diagnosis and procaine treatment of non-artlclar rheumatism. Bruxelles Medical. 16. Apr., 1950.
   Theorie general de lo douleur. Paris Medical. No. 13, 1950.
   The role of skeletal muscles in the pathogenesis of diseases. Act. Med. Scandinav. 138: 285, 1950.
   Le probleme du rhumatisms. Conception unitaire et controle par le methodes nouveeles. La Semaine des Hopit. 26: 3373, 1950.
   Some recent advances in Rheumatology. Brit; J. Phys. Med. 13: 271, 1950.
3. Hench, P. S.: B. M. J. 1949.
4. Lewis, Sir Thomas. Suggestion relating to the study of somatic pain. B. M. J. 1: 321, 1938.

INTRAVENOUS IRON THERAPY §

K. U. Jhatakia*

Iron metabolism is of interest, not only in respect to the fate of iron taken, but also in relation to the administration of various iron preparations, in the treatment of iron-deficiency anaemia. The desirability of suitable iron preparation for parenteral administration has frequently been expressed, as some patients with iron-deficiency anaemia cannot be well treated with the usual oral treatment, on account of, either poor toleration, or poor absorption.

In early days, iron was given subcutaneously or intramuscularly. These injections were painful and the preparations used were toxic. Attempts were made in recent years to find new iron preparations for parenteral use. In 1936, Ruskin and Katz tried ferrous adenylate, but it was found to be toxic. In 1945, Little and others used ferrous ascorbate intravenously but this was not found to be very satisfactory.. Hann in 1946 introduced a colloidal ferric hydroxide for intravenous use. These preparations were unsatisfactory because of their toxicity. Cappel in 1930 was the first to show that iron could be given intravenously as a saccharated iron oxide without the usual dangers of parenteral therapy. However, this knowledge was not applied clinically until Nissim[2] in 1947 reported that a solution of saccharated iron oxide was better tolerated and the iron was completely utilised in haemoglobin synthesis. Nissim and Robson[4] in 1949 gave a detailed account of the method of preparation and standardisation so as to have a uniform preparation.

The details of this method is out of the scope of this paper. They also have shown that this preparation must be standardised biologically by toxicity tests in mice. The best sample prepared by Nissim and Robson[4] had a L D. 50-300 mg. per kg. in mice. Up to 300 mg. of such samples were given intravenously in man with no toxic effects. Studies of the toxicity of saccharated iron oxide in mice revealed no evidence of any cause of death apart from precipitation of iron in the lungs, intestines, liver, kidneys and heart. The toxic effects of previous preparations produced embolic phenomena by either precipitation of the iron compound, or by the flocculation of the plasma proteins in the blood stream. The utilisation of iron given intravenously has been studied by Dubach and others in 1946 with the help of radio-active iron and also by Finch and others in 1949. In normal persons the amount of radio-active iron in the red cells steadily increased, until about two weeks after the injection 75 per cent was found in these cells, and the remaining 25 per cent presumably stored in the tissues. In patients with iron deficiency anaemia in whom both the circulating haemoglobin and the storage iron were reduced, the initial uptake of iron was quicker and the final percentage utilisation was higher. In haemochromatosis in which the circulating haemoglobin was normal and the storage iron enormously increased, the final utilisation of iron did not exceed 20 per cent while in aplastic anaemia in which the circulating haemoglobin was reduced and storage iron was normal, a similar figure was recorded. It is interesting to note the differences in the availability for haemoglobin formation of different forms of iron. Iron liberated by haemolysis is soon used up again to reform haemoglobin in preference to that from the available reserves. Iron salts given by mouth or by injection are probably as readily used for the same purpose. It has been suggested by Greenberg and Wintrobe (1946) that these two forms of iron represent a "labile iron pool" on which the first calls are made for haemoglobin formation and that the iron reserves are not drawn upon until the pool runs dry. It has also been observed that after the intravenous injection of iron in excess of that which can be bound by the plasma β-Globulin it will rapidly leave the blood stream and become part of the labile iron pool. There is however still much to be learnt about the various aspects of iron metabolism and further details about it would be beyond the scope of this paper.

---

§ Paper read at the Eighth Bombay Medical Congress, Bombay, on 25th Nov. 1950.

* Hon. Physician, Sir J. J. Hospital and Sir H. N. Hospital, Bombay.

Many papers have been published showing the effects of iron given intravenously. The preparation commonly used is a 2 per cent solution of saccharated oxide of iron, one mililitre containing 20 mg. of iron. Nissim and Robson[4] in 1949 and Slack and Wilkinson[7] in 1949 reported very satisfactory haematological response. They gave 200 mg. daily once or twice and noted practically no major reaction. It was also observed that the injected iron was nearly all utilised for haemoglobin formation except in cases with chronic infection. Govan and Scott[1] (1949) tried ferrivenin on 25 anaemic pregnant women and recorded a 1 per cent rise for every 40 mg. of iron injected. Sinclair and Duthie[6] in 1949 noted a good response to intravenous iron in hypochromic anaemia associated with rheumatoid arthritis with a low erythrocyte sedimentation rate. Various other papers have shown the results varying between a 2 to 3 per cent rise of haemoglobin per 100 mg.

I have tried this saccharated oxide of iron intravenously in about

INTRAVENOUS IRON THERAPY §

K. U. Jhatakia*

Iron metabolism is of interest, not only in respect to the fate of iron taken, but also in relation to the administration of various iron preparations, in the treatment of iron-deficiency anaemia. The desirability of suitable iron preparation for parenteral administration has frequently been expressed, as some patients with iron-deficiency anaemia cannot be well treated with the usual oral treatment, on account of, either poor toleration, or poor absorption.

In early days, iron was given subcutaneously or intramuscularly. These injections were painful and the preparations used were toxic. Attempts were made in recent years to find new iron preparations for parenteral use. In 1936, Ruskin and Katz tried ferrous adenylate, but it was found to be toxic. In 1945, Little and others used ferrous ascorbate intravenously but this was not found to be very satisfactory. Hann in 1946 introduced a colloidal ferric hydroxide for intravenous use. These preparations were unsatisfactory because of their toxicity. Cappel in 1930 was the first to show that iron could be given intravenously as a saccharated iron oxide without the usual dangers of parenteral therapy. However, this knowledge was not applied clinically until Nissim[2] in 1947 reported that a solution of saccharated iron oxide was better tolerated and the iron was completely utilised in haemoglobin synthesis. Nissim and Robson[4] in 1949 gave a detailed account of the method of preparation and standardisation so as to have a uniform preparation.

The details of this method is out of the scope of this paper. They also have shown that this preparation must be standardised biologically by toxicity tests in mice. The best sample prepared by Nissim and Robson[4] had a L D. 50-300 mg. per kg. in mice. Up to 300 mg. of such samples were given intravenously in man with no toxic effects. Studies of the toxicity of saccharated iron oxide in mice revealed no evidence of any cause of death apart from precipitation of iron in the lungs, intestines, liver, kidneys and heart. The toxic effects of previous preparations produced embolic phenomena by either precipitation of the iron compound, or by the flocculation of the plasma proteins in the blood stream. The utilisation of iron given intravenously has been studied by Dubach and others in 1946 with the help of radio-active iron and also by Finch and others in 1949. In normal persons the amount of radio-active iron in the red cells steadily increased, until about two weeks after the injection 75 per cent was found in these cells, and the remaining 25 per cent presumably stored in the tissues. In patients with iron deficiency anaemia in whom both the circulating haemoglobin and the storage iron were reduced, the initial uptake of iron was quicker and the final percentage utilisation was higher. In haemochromatosis in which the circulating haemoglobin was normal and the storage iron enormously increased, the final utilisation of iron did not exceed 20 per cent while in aplastic anaemia in which the circulating haemoglobin was reduced and storage iron was normal, a similar figure was recorded. It is interesting to note the differences in the availability for haemoglobin formation of different forms of iron. Iron liberated by haemolysis is soon used up again to reform haemoglobin in preference to that from the available reserves. Iron salts given by mouth or by injection are probably as readily used for the same purpose. It has been suggested by Greenberg and Wintrobe (1946) that these two forms of iron represent a "labile iron pool" on which the first calls are made for haemoglobin formation and that the iron reserves are not drawn upon until the pool runs dry. It has also been observed that after the intravenous injection of iron in excess of that which can be bound by the plasma β-Globulin it will rapidly leave the blood stream and become part of the labile iron pool. There is however still much to be learnt about the various aspects of iron metabolism and further details about it would be beyond the scope of this paper.

---

§ Paper read at the Eighth Bombay Medical Congress, Bombay, on 25th Nov. 1950.

* Hon. Physician, Sir J. J. Hospital and Sir H. N. Hospital, Bombay.

Many papers have been published showing the effects of iron given intravenously. The preparation commonly used is a 2 per cent solution of saccharated oxide of iron, one mililitre containing 20 mg. of iron. Nissim and Robson[4] in 1949 and Slack and Wilkinson[7] in 1949 reported very satisfactory haematological response. They gave 200 mg. daily once or twice and noted practically no major reaction. It was also observed that the injected iron was nearly all utilised for haemoglobin formation except in cases with chronic infection. Govan and Scott[1] (1949) tried ferrivenin on 25 anaemic pregnant women and recorded a 1 per cent rise for every 40 mg. of iron injected. Sinclair and Duthie[6] in 1949 noted a good response to intravenous iron in hypochromic anaemia associated with rheumatoid arthritis with a low erythrocyte sedimentation rate. Various other papers have shown the results varying between a 2 to 3 per cent rise of haemoglobin per 100 mg.

I have tried this saccharated oxide of iron intravenously in about

Case No.	Sex	Age.	Clinical. Etiology.	Bone Marrow.	R. B. C. Count in millions per c.mm.	Hb. in Gm. per 100 c.c.	Total amount given in cc.	During No. of days	Max. amount tolerated at a time.	Final R.B.C per cmm.
1	M	30	Bl. piles.	Hyper N‡	3.0	6.5	55	12	5.0	4.7
2	M	35	,,	Macro N††	2.7	6.8	60.5	15	5.0	5.3
3	M	52	,,	Hyper N††	1.4	3.74	90	20	5.0	3.8
4	M	35	Dh.*	,,	0.8	1.7	100	22	5.0	2.2
5	M	26	Nephrits.	N††	1.6	6.46	108	24	5.0	3.2
6	M	25	Bl Piles.	N††	2.48	9.52	84	17	5.0	3.5
7	F	35	Menorrhagia.	N†	1.6	5.1	100	24	5.0	3.2
8	F	40	Menorrhagia.	N††	1.4	3.26	141	18	10,0	3.0
9	M	50	Bl. Piles.	Hyper N††	1.6	3.4	105	14	10.0	2.6
10	M	45	,,	N††	2.2	5.4	95	15	10.0	4.2
11	F	40	Dh.*	N††	2.6	6.8	205	18	10.0	4.5
12	M	30	Bl. piles.	N††	1.8	5.1	145	16	10.0	3.8
13	F	20	Dh.*	N††	2.9	8.16	105	12	10.0	3.4
14	F	30	,,	N††	2.6	8.5	100	14	10.0	3.6
15	M	35	Bl. Piles.	N††	1.7	3.4	72	16	10.0	4.2
16	M	38	Dh.*	N††	1.8	5 1	50	8	10.0	3. 15

* Dh. Dyshaemopoetic

† Hyper: Hyperplastic

‡ N Normoblastic

Final Hb in grams per 10 c.c.	Rise in RBC Total.	Total rise in Hb in grams.	Average Hb rise per 100 mg. of Iron.	Average Hb rise per day during treatment.	Dilution used.	Imp. Toxic Effects observed.	Remarks.
10.5	1.7	4.5	2.5	2.25	10 c.c. Saline.	Vomiting once. Slight chill.	Oedema cleared up.
13.0	2.6	6.2	3.2	2.5	10 cc.. Saline.	..	....
8.8	2.4	5.06	1.7	1.5	10 c.c. Saline.	....	For 10 days he was given nothing but rice.
7.5	1.4	5.7	1.5	1.6	"	....	Case of Hyper splenism.
10	1.6	3.5	1	1	40 c.c. Glucose.	Drop in B. P. Giddiness Heavy head Body aches.	Albuminuria ++ B.P.++
13.0	1.0	3.5	1.2	1.2	10 c.c. N. Saline.	Rigor on 1st day.	Operated for Hydrocele later on.
9.2	1.6	4.2	1.25	1.2	10 c.c. Glucose.	Urticaria Giddiness.	
8.5	1.6	5.3	1.1	1.7	20 c.c. Glucose	Flushing of face; restlessness; nervousness in 3rd 10 c.c. dose. No reaction later in same dose.	
8.5	1.0	5.1	1.5	2.2	Hb 10.3% Ampules π equal amount.	Temp. upto 103 and then 100 for 1st 3 days.	
12.0	2.0	6.6	2.2	2.6	10 c.c. Saline 10 c.c. D. Water.	Palpitations, pain in chest, giddiness in 10 c... dose.	Headache persisted till Iron was given.
13.6	2.0	6.8	1.0	2.2	15 c.c. N. Saline.	Nausea Uneasiness. Temp. rise for 1 day.	10 c.c. twice a day in last 8 days.
11.0	2.0	6.0	1.2	2.2	equal amount. of D Water.	..	....
10.2	0.5	2.0	0.6	1.0	D. Water equal amount	Nausea Vomiting Abd. pain giddiness in 10 c.c. dose.	MCV 100 MCH 28.5 MCHC 28.5% Hypoproteinemia Alb. 2.5 Gl. 2.4 Tpy. 5%
11.9	1.0	3.4	1.0	1.4	Glucose eq. amt.	Flushing uneasiness Tingling in limbs Temp.	
9.35	2.5	6.0	2.5	2.2	in 10 c.c. Glucose	Local Burning.	
9.5	1.4	4.4	2.5	3.5	10 c.c. Glucose.		

1 c.c. Uniferon contains 20 mgm. of Iron.
1% Hb. rise=0.17 gms. Hb.

40 cases by now, but the results of treatment of only 16 cases are reported here. All these 16 cases were from our unit at the Sir Hurkisondas Narottamdas Hospital, Bombay. In each of these cases, a thorough clinical history was taken and a complete haemotological examination including absolute indices and bone-marrow studies was carried out. Only those patients who showed both mean corpuscular haemoglobin and mean corpuscular haemoglobin concentration below the normal range were given this therapy. Thus these anaemia cases were of hypochromic and hyposaturation type. The bone-marrow in all these cases showed a normoblastic picture. In the beginning I did not restrict the use of this therapy to those who were either resistant to oral iron or who did not tolerate it, as I wanted to study the general tolerance and effectivity of the preparation used. The preparation which was used in all these cases was 'Uniferon' prepared by a local firm. This series of 16 cases represents various types of iron deficiency anaemias. Out of the 16, the males numbered 11, the females 5. Age varied from 20 to 52 years. Among the males, the etiology in 8 cases was bleeding piles, in one subacute nephritis, in one hypersplenism, while in one, nutritional dyshaemopoesis was the probable factor. Among the female patients menorrhagia was responsible in 9, while nutritional deficiency was the probable cause in the rest. In each case on the first day a test dose of 1.5 cc. i.e. 30 mg. of elemental iron was slowly administered well diluted in 5 cc. of glucose or normal saline. The dose was raised to 3 cc. on the second day and to 5 cc. on the third day. Later on, in some, 10 cc. was given once and in one case in this series 10 cc. was given twice a day. The drug was diluted with various fluids. The iron solution is highly alkaline, its pH value being about 11.0. If it is injected undiluted it produces venous irritation and even thrombosis. In the beginning it was diluted with an equal amount of a 0.3 per cent hydrochloric acid solution but this often produced fever and giddiness. Then the drug was diluted with equal amounts of either 25 per cent glucose solution, normal saline or distilled water. This decreased the incidence of side reactions. Whenever a patient developed a side reaction, the next day the drug was diluted with a larger quantity of diluting solution and thus reactions were minimised The rate of injection should be slow to avoid a burning sensation in the veins and other side effects such as giddiness and shock.

The daily dose:—In 7 cases a maximum daily dose of 100 mg. was given in a single injection while in 8 cases 200 mg. was given once daily while in one 200 mg. was given twice a day for a few days. With 200 mg, mild side effects were oberved on the first day in few cases.

The total dosage varied from 1000 mg. to 4000 mg. in a period of 8 to 24 days. No signs of metallic intoxication were noted in any one till they were discharged.

Therapeutic effects:— As intravenous iron is quantitatively converted to haemoglobin, it should be possible to calculate the amount of iron required to raise the haemoglobin percentage to normal. Theoretically 100 mg. of elemental iron should increase the blood haemoglobin by 0.55 Gm. or 3.2 per cent. But this is not so in chronic iron deficiency anaemia as the iron reserves are depleted to an unknown degree. Slack and Wilkinson[7] suggested that 50 per cent should be added to the calculated iron requirement in order to raise the reserved iron to normal. It will be remembered here that 1 Gm. of haemoglobin contains 3.34 mg. of iron and that about 25 mg. of iron are required to increase haemoglobin concentration by one per cent under the best conditions. It will also be interesting to note here that the utilization of iron given orally as ferrous salts varies as from a 3 to 20 per cent maximum, while given intravenously it is about 100 per cent.

In this series, 100 mg. or 200 mg. of the drug was given daily for a few days and the effects were noted. The total R.B.C. and Hb rises were recorded in relation to the quantity given. From this I calculated the average haemoglobin rise per 100 mg. of the drug and also calculated the average haemoglobin rise per day, to know whether bigger doses could reduce the relative duration of treatment. The findings in these cases were as follows. In this work 17 Gm. was taken as equivalent to 100 per cent of haemoglobin.

The average Hb per cent rise per 100 mg. of drug was 3.2 per cent in one case, between 2.5 and 3 per cent in 3 cases, between 2 and 2.5 per cent in one case, between 1 and 2 per cent in 10 cases while below 1 per cent in one case. The best effect was in recently developed iron deficiency anaemia as a result of bleeding piles while those with chronic iron deficiency had a comparatively poor response.

While calculating the average daily rise in the percentage of haemoglobin, it was observed that in 8 cases the daily rise was between 1 and 2 per cent, in 7 it was between 2 and 3 per cent while in one the daily rise was of 3.5 per cent. This shows that one can shorten the duration of treatment in suitable cases with this method by using bigger tolerated doses. Each case in this series had more than a 1 per cent rise in Hb. This is important as by the oral method the rise in Hb per day is rarely more than 1 per cent, as orally, more iron is either not well tolerated or absorbed or utilised. The intravenous route is chiefly recommended in those cases where oral iron is either not effective or not tolerated. For such cases it is really a good advance. I will give a brief review of a few such cases, along with the graphs.

In one case where there was a chronic iron deficiency, Blaud's mass gr., 20 twice a day was tried first and one blood transfusion was given. The patient had also liver extract with vitamin B complex previously. With this regime for 30 days the blood count did not show any improvement. He was then given intravenous iron totally 100 cc., i.e. 2000 mg. in 22 days. At the end of this period the R.B.C. count increased from 0.8 million per cu.mm. to 2.2 million, and the Hb. from 10% to 45%. The haemoglobin rise for 100 mg. of iron was 1.5% and the average daily rise of haemoglobin was 1.6%. As he went home against advice further treatment could not be carried out.

Another case had generalised edema, cardiac dilatation, a blood pressure of 155|120, marked albuminuria with red blood cells and casts in the urine. The blood urea was 93 mg. per 100 cc. He had orally administered iron at first but as it was not well tolerated, intravenous iron was given. A total of 108 cc., i.e. 2160 mg. of iron was given in 24 days. The total R.B.C. rise was 1.6 million per cu.mm. and Hb rise was 3.5 grams. Thus there was a one per cent rise of hæmoglobin per 100 mg. of iron. He tolerated the iron very well except on the first day when he had a headache, and a fall in blood pressure. 5 cc. of iron solution was then diluted in 40 cc. of glucose solution and the patient had no untoward reactions. At the end of 24 days he showed a general improvement, the edema cleared up, the blood urea came down to 58 mg. per 100 cc. and the urine picture also improved. He had only an alkaline mixture with this therapy. The general improvement must be due in part to the improvement in the anaemia. This case has shown that in such kidney lesions, iron, even though a heavy metal, is well tolerated. This may be due to the fact that the urinary excretion of iron is very insignificant and the chances of irritation to the kdineys are few.

The two cases just quoted illustrate the effect of iron given intravenously in the respective conditions.

Reticulocytic response:— This was observed within 3 to 6 days and varied from 4 to 15%. A daily reticulocyte count was not done in all these cases. In chronic iron deficiency the reticulocyte response was delayed.

Toxic reactions:— The common toxic effects reported include rigors, collapse with fall in blood pressure, tachycardia, dyspnoea, cyanosis, chest and back pains and diarhoea. These effects are more common with bigger doses. With ferrivenin and with the preparation of Slack and Wilkinson[7] the safe upper limit seems to be 200 mg.

of iron per injection.

With certain samples, impurities in the sugar of saccharated iron oxide appear to be responsible for the toxic reaction. These reactions are of rapid onset, transient duration and are free from sequelae.

In 2 cases not included in this series, the patients had severe headache, vomiting, giddiness and rise in temperature on the first day. As they did not take any more injections on the second day, the treatment had to be abandoned.

In this series, reactions were found in 11 cases. The common toxic effects were as follows:—

Nausea	.. 3	Headache	.. 4
Vomiting	.. 2	Giddiness	.. 4
Diarrhoea	.. Nil	Nervousness & restlessness	2
Fever	.. 3	Generalised pains	.. 2
Flushing of face.	.. 2	Chest pain	.. 1
Burning along the vein	.. 1	Tingling in extremities	.. 1
Urticaria	.. 1	Venous thrombosis	.. Nil
Palpitations	.. .	Drop of blood pressure	.. 1

Most toxic effects were mild except the temperature rise in 3 cases which went up to 101°F. on the first day but settled down within 8 hours. The toxic effects were minimised by using higher dilutions. The reactions were mostly found on the first day and then the patient tolerated the drug well. No untoward reaction of any major significance was noted in this series. No cumulative toxic effect was observed in any case after prolonged therapy with a total dose amounting to 4000 mg. in one case within 18 days. A 200 mg. twice a day has been given in some cases with good tolerance.

CONCLUSION

This is preliminary report on intravenous iron therapy and the number of cases is small. However, from the few observations it seems that this therapy is really a good advance in the treatment of patients with iron deficiency anaemia, who either do not tolerate or absorb iron properly.

This method reduces the treatment period in some suitable cases, as a rise of haemoglobin up to 4 to 6 per cent per day may be achieved.

The toxic effects are not of much significance and most cases tolerate the drug very well. Even with kidney lesion the tolerance is good thus showing that iron in this form is not so strong a poison as it is thought to be.

Theoretically 100 mg. of iron should raise the haemoglobin by 4 per cent but in practice we have not obtained that figure. Yet the results are fairly good. The average daily rise of haemoglobin is better than that achieved by the oral route.

In spite of all these, I would say that this intravenous iron therapy is best suited to patients in hospitals where the rapid rise of haemoglobin will shorten the hospital stay and so the cost. This is not so for patients treated in private practice as it will be more costly in such conditions. However, in all, where tolerance or absorption is at fault this is the ideal therapy. This therapy should not replace oral therapy in the ordinary run of cases but should be reserved for suitable subjects.

My thanks are due to Dr. B. B. Yodh of our unit at Sir H. N. Hospital who gave me a free hand for this work, to the Sir H. N. Hospital authorities for allowing me to publish this and to the Housemen attached to our unit for their help. Lastly I thank Mr. Mody of Unichem Laboratories for liberal supply of the drug "Uniferon" for the trial.

REFERENCES

1. Govan, A. D. T. and Scott, J. M.: Intravenous iron in treatment of anaemia of Pregnancy, Lancet, 1: 14-16, 1949.
2. Nissim, J. A.: Intravenous administration of Iron, The Lancet, 2: 49-51, 1947.
3. Nissim, J. A. and Robson J.M.: Intravenous treatment of anaemia with an iron-sucrose preparation, The Lancet, 1: 326-327, 1949.
4. Nissim, J. A. and Robson, J. M.: Preparation and standardization of saccharated iron oxide for intravenous administration, The Lancet, 1: 686-689, 1949.
5. Robson, J. M. and Keele, C. A.:—Recent Advances in Pharmacology, Pg. 269-285, J. A. Churchill, London, 1950.
6. Sinclair, H. G. B. and Duthie, J. F.: Intravenous iron in hypochromic anaemia associated with rheumatoid arthritis. The Lancet, 2: 646-648, 1949.
7. Slack, H. G. B. and Wilkinson, J. F.: Intravenous treatment of anaemia with an iron-sucrose preparation, The Lancet, 1: 11-14, 1949.

RECURRENT DIARRHOEA IN CHILDREN §

B. D. Patel *

In spite of the advent of effective chemotherapy and antibiotics, recurrent diarrhoea presents a serious problem to the pediatrician. Such diarrhoeal complaints are encountered throughout the year. The lack of reliable accounts from the parents regarding the frequency of attacks and to a certain extent their inability to procure and at times to take adequate treatment has hampered both the preventive and the curative aspect of the problem. In order to ascertain the factors influencing the recurrent diarrhoea an attempt has been made to analyse case reports of the patients that were admitted at the Byramjee Jeejeebhoy Hospital for Children from October 1949 to September 1950.

CLASSIFICATION

Reference to Table I shows that during the one year under review 2381 patients were admitted to the hospital. 569 (24%) patients were found to be suffering from diarrhœal symptoms and of these 221 (39%) could be said to be suffering from chronic diarrhœa. These can be classified into two groups, (a) those admitted with a definite history of frequent gastro-intestinal upset, and (b) those with complaints of other systemic disorders. 54 per cent of the chronic diarrhœa cases belonged to the first group, while 46 per cent belonged to the second. Thus it is very significant that both groups have an almost equal incidence. The patients belonging to the second group have a silent infection of the bowel. In them it was not possible to ascertain the origin of the disorder. However this silent process occasionally flared up into an acute phase.

TABLE I

Total admissions	2381	
Patients with diarrhoea symptoms	569	24%
Chronic diarrhoea patients	221	39%

Microscopic examination of the stools of all these patients were carried out on more than one occasion. Because of the difficulty of getting fresh stools the rectal swab method as described by Coelho[1] was largely used. The following table shows the results of these examinations obtained in all the patients suffering from recurrent diarrhoea.

---

§ Paper read at the Bombay Medical Congress, 1950.

* Byramjee Jeejeebhoy Hospital for Children.

TABLE II

Total	B. Dyst.	Giardia	Worms	F.Glb.	Pus cells	Amoeba
221	72(32%)	62(28%)	52(23%)	14(7%)	18 (9%)	3(1%)

Classification of these patients bacteriologically is not possible as we have no facilities for this purpose. We have to rely on the stool and the clinical examination for determining the causative factor. The presence of macrophages in the stools has been taken as an indication of bacillary infection. Pus cells have been found in some stool reports without any further abnormality and these cases have been classified separately. On the basis of these criteria, recurrent diarrhœas have been found to have the above-mentioned incidence. Bacillary dysentery has been responsible for the maximum number of cases—72 (32%). Giardia infection is next—62 (28%) and helminthic infestation follows, with 52 (23%). Of the latter about 20 per cent were due to infestation by round worms. Fat globules were present in the stools in 7 per cent of cases. It is not possible to advance the exact explanation of this abnormal finding but dietetic errors, idiopathic coeliac disease, vitamin deficiency, pancreatic insufficiency, chronic nutritional failure and tabes mesenterica may have to be thought of in the explanation of this finding. Pus cells alone were found in 18 per cent of these cases and all these were admitted for other systemic symptoms and only on routine examination of the stools were pus cells discovered. Since they were persistently present in the repeated stool examinations their significance cannot be ignored. It may be argued that these were cases of a silent affection of the intestinal tract which may have been caused either by infective processes or they may be the cases which would fall under the group of ulcerative colitis. Amoebic dysentery was present in only 1 per cent of cases. This emphasizes the low incidence of this type of infection in the younger age groups.

Out of the 221 cases 63 per cent were male and 37 per cent female children. The relative frequency of chronic diarrhœa at various age groups is indicated in Table III.

TABLE III

Age—Years	1	2	3	4	5	6	7	8	9	10	11	12
No. Patients	63	45	39	17	16	4	7	5	8	8	4	5
Percentage	29	21	13	8	8	2	3	3	4	4	2	3

The incidence is highest in the first year and declines with age. The number in the first year is four times that among children five years old. The incidence after the fifth year is small.

Table IV shows the incidence of chronic diarrhœa during the various months:

TABLE IV

Jan.	Feb.	Mar	April	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
22	13	22	23	17	9	17	12	2	23	22	29

The first and last quarter has an almost equal incidence while the second and third quarter are responsible for only a small percentage of recurrent diarrhœas. These are the months during which the incidence of acute diarrhœa is found to be high while that of the chronic type is low. This anomaly may be explained on the basis that recurrences in this season have a tendency to be severe, probably because of a super-added infection; hence these patients may be admitted as acute cases. Besides that, the history we obtain from our patients is often defective. The high incidence of chronic diarrhœa in the last and first quarter is due to a carry-over of the monsoon infections. The seasons have no particular significance.

PRESENTING SYMPTOMS

Table V indicates the main presenting complaints. Of these 221 patients, 106 (48%) were admitted with the history of stools, 27 (12%) with vomiting and 14 (6%) with a history of abdominal pain. Those patients who were admitted for non-diarrhœal complaints had a very varied list of presenting symptoms. These included fever, cough and fever, loss of appetite, loss of weight, general debility, dyspnœa, night-blindness and convulsions.

TABLE V Common presenting symptoms

Fever	.. 118
Cough	.. 107
Frequent stools	.. 106
Distention of abdomen	.. 50
Vomiting	.. 27
Pain in abdomen	.. 14
Loss of appetite	.. 10
General weakness	.. 5
Convulsions	.. 4
Worms	.. 4
Crying	.. 3

CLINICAL FINDINGS

The majority of these patients looked emaciated with an absence of subcutaneous fat. All the patients without exception were markedly underweight and this is illustrated in the Table VI where the actual weight of the patients investigated is seen in the second line while the expected weight is seen in the third. Avitaminosis was a very noticeable feature in all these children. In all there were multiple deficiencies but the symptomatology of vitamin B complex defi-

TABLE VI

Age in years	1	2	3	4	5	6	7	8	9	10	11	12
Average wt. of patients in lbs.	11.4	15.5	17	20	24½	27	27	25	40½	42½	38	48
Expected wt. in lbs.	21	28	33	37	41	45	49	54	59	64	69	74

TABLE VII Associated Findings

Disorders	**No. of cases.**
Anaemia	.. 199
Rickets	.. 145
Malnutrition	.. 114
Vitamin A : B deficiency	50 : 48
Lung complications	.. 38
T. B. infections	.. 29
Oedema of legs	.. 27
Stomatitis	.. 23
Hypotonia	.. 19
Photophobia	.. 8

ciency dominated the picture. This consisted of the well-known glossitis, angular stomatitis, pigmentation, tendency to diarrhoea, changes in the hair and tendency to clubbing of finger and toe nails, particularly the former. A few children, who were in an advanced stage, had dilated hearts, tachycardia, enlarged livers, oedema of hands and feet and even ascites. Xerosis and phrynoderma, the signs of vitamin A deficiency were present in over 50 per cent of our cases. Bitot's spots were seen in less, and so also keratomalacia. Perhaps because of the age, we were not able to elicit a history of night blindness in a greater number of our children who had evident signs of vitamin A deficiency. Scorbutic manifestations in the form of bleeding gums, and subperiosteal haemorrhages were also infrequent in this series. We did not have facilities for the estimation of ascorbic acid in the blood nor was it possible to take roentgenograms of the bones for evidence of scorbutic changes. Yet in those children who had oedema, it was not uncommon to find purpuric spots round the hair follicles on the outer aspects of the legs and fore-arms. A very large percentage of our hospital infants suffer from rickets. Hence one cannot place the relation of this condition to rickets. The abdomen was enlarged in some cases. This was due to gas in the intestines and general hypotonia. In some the abdomen was doughy. Tenderness on pressure was unusual though many chilren were brought with a complaint of pain in the abdomen. This pain was in nearly all cases referred to the umbilicus. In some the abdomen was also flat and retracted. This was due to a tubercular abdomen and marked wasting.

A constant finding on palpation of the abdomen was the enlarged liver. Though normally the liver may be palpable below the costal border in the first year of life, yet in all these children, the size was greater than could be normally expected. The liver was smooth, soft, and with an edge that was not sharp. Only when the feel was on the harder side did the edge become sharper. There was no tenderness of the liver.

The spleen was palpable, particularly when anaemia was present.

The blood invariably presented the picture of an anaemia. In the majority of cases it was of a hypochromic variety. The red blood cell counts were below three millions per ml. in 60 per cent, between 2 and 3 million in 20 per cent, between 1 and 2 millions in 15 per cent and less than one million in 5 per cent The haemoglobin has been on the average between 40 and 60 per cent in the majority of cases. There have been some children whose red blood cell counts have been round about one million or 900,000 per ml., haemoglobin about 15 to 20 per cent and colour index above 1. This has been a feature particularly with infants who besides diarrhœa had marked signs of vitamin B complex deficiency, especially the glossitis and pigmentation. Such cases predominate in the last quarter of the year. A few of such children may have petechial haemorrhages. Whether these are due to vitamin C deficiency, P factor, or a lowered tissue vitality is difficult to say. But in none of these did we find any thrombocytopenia.

The leucocytes were generally increased, even in the absence of dehydration, which discounts the possibility of a haemoconcentration as an explanation for the leucocytosis. The differential count had nothing characteristic, perhaps in a few cases with macrophages and acute exacerbation, the polymorphonuclear cells had risen to about sixty per cent. Further round worm infestation was found in 52 cases but in none of these was there a rise in the eosinophilic cells. This upsets the point often stressed in the differential diagnosis of ascarias infection.

STOOLS

The number and character of the stools varies in these cases. The majority of them had more than four stools with fluid or semisolid consistency, while others had fewer and well-formed stools. However, the stool examination of the patients gave positive abnormal findings. Thus the stools of these patients may broadly be divided in two groups. Firstly, of those who had small, frequent, semi-solid stools with blood, mucus and pus cells in it. This group of children also had abdominal pain and tenderness. The majority of these children were found to be suffering from bacillary dysentery. The other group had fewer, but bulky, whitish and offensive stools. Straining and abdominal pain were often absent. This group usually belonged to the coeliac syndrome. Dehydration was found in 50 cases. Only in a few was it of a serious degree, requiring immediate hydration therapy. Vomiting was not present to any extent. Consequently the dehydration may be said to have resulted from the frequency of stools of long duration. Some cases may also have resulted from deficient water in-take. In these cases loss of appetite was a dominant feature. With a mild degree of dehydration only a loss of turgor was found, while with a moderate degree of dehydration, sunken and listless eyes, dry furred tongue, and inelastic skin were present. The last feature was exaggerated by the marked degree of malnutrition that was found in many of them. In dehydration of the most severe character, cold and clammy feet, tachycardia, soft and thready pulse, restlessness and constant crying were additional features.

The history of pain, in the younger age group remained vague and unsatisfactory because of the difficulty in eliciting this information. In some cases, it was complained of frequently with no definite localisation, while others pointed to the para-umbilical and descending colon regions. This type of pain tended to be colicy in nature with frequent evacuation of the bowel. These patients also passed offensive flatus frequently. Many of them belonged to the bacillary dysenteric group of infection. A doughy abdomen was present in a fair number of patients. Most of the children with worm infestation and tubercular abdomen had this feature. Its recognition should always remind one of the above mentioned conditions in recurrent diarrhoea.

Clubbing of the fingers was found in 86 patients, about 16 per cent. Its association with dysenteric infection is well known. It may be that in these patients the combined effect of toxicity and vitamin B deficiency may be responsible for its occurrence.

DISCUSSION

In a very large number of these children a focus of infection outside the alimentary tract was present. Table VII indicates the common associated findings. This formidable list emphasizes the importance of a thorough and careful clinical examination particularly from the preventive aspect of the treatment.

Our limited facilities allowed only a few investigations. The importance of the rectal swab emphasised by Coelho[1] is supported by our observations. The bacteriological investigation is necessary to establish the causative factors.

Vitamin A and B deficiencies have been found in a large proportion of our patients. Ramalingaswami[8] (1943) observed that in a group of patients with vitamin A deficiency diarrhœa responded specifically to vitamin A therapy and chemotherapy was ineffective. These diarrhœas were non-infective in nature and responded poorly to bismuth carbonate and kaolin mixtures. In his series of 20 cases vitamin A estimation gave a low value in 6 cases. All the 20 patients of his series had diarrhœa and ocular symptoms. Photophobia, lacrimation, and irritation were present in 14 cases. It is also reported by others that diarrhœa occurs in advanced cases of vitamin A deficiency. Only a few patients had keratomalacia and Bitot's spots in our series, while dry skin, phrynoderma and xerosis were found more commonly.

Interesting changes in the mucosal lining of the small intestines have been described. Atrophy of the villi of the small intestine have been reported and occasional keratinoid changes recorded as well. Vitamin A administration seems to bring about clinical and histological cure in these patients. While neither vitamin A deficiency estimations of the blood nor the post-mortems of the patients in our series are available, it may be presumed that in a fair proportion of our patients similar changes may be in existence.

Many of our patients had pigmentation, glossitis and other signs of vitamin B deficiency. The occurrence of diarrhœa in pellagra is well-known and with the high incidence of this vitamin deficiency in our patients its etiological importance cannot be ignored. Further, malnutrition was found in large proportion of cases. This high incidence with multiple deficiency factors lowered the resistance of these patients and exposed them to high morbidity rate. Their power to combat infection was lowered and each attack left the child more vulnerable. This lowered resistance may also give rise to the increased incidence of the upper respiratory tract infection which was found to be high in our series. Tuberculous infection was present in 29 cases. Tuberculous infection of the alimentary tract in our children is well recognised. The lesions in the small intestines and the blockage of the lymphatics by the tuberculous processes in the abdomen, may give rise to recurrent diarrhœas without any abnormal findings in the stool.

Liver enlargement beyond the limit of normal was found in 18 per cent of cases. This high incidence merits careful observation and assessment of liver damage in these patients. In only three cases the diagnosis of cirrhosis of the liver was recorded. Enlargement of the liver, jaundice, and haemorrhagic complications have been described in patients with infantile diarrhœa by Wainwright.[3] He observed that pathological changes in the liver are not well defined nor are they constant and they do not fall in any particular well defined group. Dilatation of the sinusoids, cellular necrosis, parenchymal degeneration, fat infiltration and cell infiltration with early fibrosis in some cases have all been observed in diarrhoea patients. However, fat infiltration is much more common in infants than in adults, being found in about 50 per cent of necropsies. This is presumed to be related to the nutritional state of the infant, emaciated infants, displaying scanty changes. Thus the fat infiltration in patients with diarrhœa may be toxic in origin or due to a deficiency of protein which contains the important lipotrophic substances. It is not possible to state the reason for the enlargement of the liver in our recurrent diarrhœa patients as post-mortem and liver biopsy observation were not available. However from the high incidence of malnutrition and deficiency factors that were found in our series it may logically be presumed that the changes as described in literature may have been responsible for the pathological enlargement of the liver. Also the toxins reaching the liver by the blood stream from the alimentary tract may be responsible for its enlargement in some patients. The interesting feature would be to ascertain the extent to which the recurrent diarrhœa may be held responsible for the initiation of cirrhotic changes in the livers of our children.

Food allergy may have to be considered as a causative factor though in our series this could not be elicited. The recognition of the offending material will have to be sought for and this none too easy task may present a formidable problem. The group of diarrhœas belonging to steatorrhœa will often present a problem for investigation. In the stool examination the fatty abnormality should be investigated for the recognition of digestive and absorptive defects of the alimentary tract. In our recurrent diarrhœas unless these additional methods of investigation are resorted to the incidence is not likely to be influenced materially.

TREATMENT

In order to combat the recurrent infection of the gastro-intestinal tract, effective and well tried chemotherapeutic agents were used. In our cases of acute exacerbations of the recurrent diarrhœas we have administered sulfadiazine with very satisfactory results. This drug is well tolerated in our experience and it has not produced the dreaded complications. Formo-cibazol and thalazole were used frequently in prolonged recurrent diarrhœa. As these are not absorbed to any large extent from the alimentary tract they can be given in adequate doses even in cases of dehydration and anaemia. Enterovioform and similar drugs when combined with sulfadiazine were found very effective in cases where the latter alone did not prove effective. The hydroxyl-quinoline group of drugs are known to exert their effects on the pathological flora of the small intestines in addition to the Entamoeba histolytica.

Sulfasuxidine and sulfaguanidine have not been found effective in our experience. Patients who belonged to the ulcerative colitis group and who did not respond satisfactorily to oral sulfa therapy were successfully treated with the rectal administration of these drugs. We have found sulfadiazine and thalazole when given rectally produce very satisfactory results. This drug may be given suspended in tap water or in normal saline. The retention enemas are better retained if a rectal lavage is carried out prior to the administration of the drug. The raising of the foot of the bed and the strapping of the buttocks have proved useful. It is presumed that by allowing the drug to come in contact with the site of the lesion in greater concentration a better therapeutic effect is obtained.

The newer antibiotics should be given fair trials in recurrent diarrhœas. When the above mentioned drugs did not yield satisfactory results streptomycin orally has proved of considerable use. The good effect of aureomycin in virus diarrhœas and amœbiasis has already been stressed.

Mepacrine was given for the cases of giardiasis. It may be mentioned that we are administering oleum chenopodium 1 minim for each year of age in combination with castor oil to all our patients with round worm infestations. Our results are satisfactory, but other remedies such as santonin and diphenan may be given if indicated. Hetrazan is being used in cases of worm infestation. In our limited experience this drug has not given more satisfactory results.

Diet: An initial period of starvation was resorted to in those patients who had an acute exacerbation of the chronic diarrhœa. Weak tea and banana pulp were given in this initial stage for a period of 24 to 48 hours and thereafter skimmed milk or protein milk was introduced gradually in increased quantities daily. In the majority of our malnourished children with frequent stools protein milk was started from the time of admission and full diet commenced at the first opportunity. The diet was supplemented with meat juice and amino acid preparations in all the malnourished children. As some of these patients had anorexia and as quite a large number of them are known to have hypochlorhydria, hydrochloric acid mixture was given for its appetising and digestive effects. It also has the additional advantage of preventing pathological organisms reaching the lower intestinal tract. Digestive enzymes and extracts of stomach and pancreatic factors should be given for enhancing digestion.

Folic acid, crude liver extracts, vitamin B complex and vitamin A were given parenterally as majority of these cases were suffering from multiple deficiency factors.

Repeated blood transfusions and protein hydrolysate intravenously were given to improve the general health of patients. Dehydration should be treated with the usual glucose saline solution.

Every effort should be made to prevent the recurrence of attacks. As an unhygienic condition of the hand is known to predispose to recurrent diarrhoea parents should be instructed in the elementary hygienic principles. Many of these cases of recurrences also result from ineffective and incomplete treatment. Further, chemotherapy by producing quick clinical improvement has hampered the complete eradication of the infection. Consequently in preventive measures these factors should not be lost sight of. Lastly, foci of infection outside the alimentary tract should be carefully searched for and eradicated as their persistence is often associated with the recurrence of the gastro-intestinal upset.

REFERENCES

1. Coelho Eric: Rectal swab in the investigation of diarrhoea in children, Ind. J. Med. Sc., 3: 266-271, 1949.
2. Ramalingaswami V: Nutritional diarrhoea due to vitamin A deficiency, Ind. J. Med. Sc., 2: 665-674, 1948.
3. Wainwright J. Hepatitis associated with infantile diarrhoea, Arch. Dis, Child., 25: 296-291, 1950.

PARENT CHILD RELATIONSHIP

J. C. Marfatia *

IMPORTANCE OF THE SUBJECT

Parent-child relationship forms the crux of the whole problem of child psychology. There are not many views in both adult and child psychiatry, on which there is general agreement. There is, however, almost universal agreement among psychiatrists regarding one thing, viz., that the first five or six years of life is the formative period during which the foundation is laid for the development of an individual's personality. It is this foundation on which the super-structure of future personality development will be constructed. During this formative period the child is in closest association with his parents, who form his immediate world The child's mind is plastic. That is not to say that the child is passive throughout and allows his personality to be moulded like shapes moulded out of clay, but faulty habits and reaction-formations have not yet taken root which fact allows for pliability. One can easily understand how, given such a plastic mind, the attitudes of parents who form the immediate environment, can shape the character and personality of the child.

For the development of a healthy and well integrated personality there are certain fundamental emotional needs of the child, which must be satisfied. Just as a deficiency of vitamins in the child's diet leads to disturbances of physical growth, so also the non-satisfaction of the fundamental emotional needs of the child leads to faulty development of the mental growth, which may subsequently manifest itself in the form of behaviour problems. If these behaviour problems, which indicate faulty patterns of adjustment, are not detected and treated early, they may lead to the development of a neurotic personality which may, later on in life, with further environmental stress, break down into a frank neurosis or psychosis.

The most fundamental emotional needs of the child are:—

1. The need for stable and secure parental love.
2. The need for recognition and response.
3. The need for approbation.
4. The need for emotional growth.
5. The need for play and companionship.
6. The need for having a concrete ideal in the home after whom the child can mould his own personality.

A careful study of the list shows that the satisfaction or otherwise of these needs depends entirely on healthy and normal parental attitudes towards their children.

---

*Hon. Psychiatrist, Sir Jamshetjee Jeejeebhoy Hospital, Bombay.

Some of the faulty parental attitudes, which form one of the most outstanding causes of neurotic and behaviour disturbances in children, are as follows:

Overprotection or over-acceptance, rejection which includes punishment, partiality and favouritism, unnecessary and unfavourable comparisons, a too disciplinarian attitude as indicated by over-domination, the expecting of implicit obedience from the child in every little matter, nagging, the exacting of too much work, pushing at studies, inconsistency in discipline, discord between parents and neurotic attitudes of grandparents.

Each one of these harmful attitudes will be discussed briefly.

OVERPROTECTION

The criteria laid down by David Levy[3] in order to label a particular behaviour on the part of the parents as over-fondling or babying are:—

(1) Excessive contact of mother with the child; (2) Prolongation of infantile care, i.e., delayed weaning and bottle feeding for an unusually long peroid; dressing and bathing him long after he is able to take care of himself; (3) Prevention of development of independent behaviour, i.e., the mother may fight the child's battles for him: (4) Lack or excess of maternal control.

There are parents who cannot refuse any requests of children, however, unreasonable they may be. They give money, toys, special privileges, and spend all possible time with the child. They do not want him to leave for recreation lest he meet with an accident or associate himself with 'undesirable' companions. The child sleeps on the same bed as the parent. Some parents not only fail to see any fault in their child but defend him even though he may be in the wrong. They praise him to the skies in the presence of others. Sometimes overprotective behaviour is shown by over domination.

The results of overprotection—When overprotection is characterized by over-domination, submissive traits are developed. The child may become overdependent, obedient, authority-accepting, and effeminate He finds the over-sheltered life so pleasing and satisfactory that he is not inclined to make social contacts in the outside world which he does not find as sympathetic and kind as his parents who form his immediate world. He finds adjustment, outside his home, extremely difficult. He may fail to adjust at school and later on at work. He becomes increasingly withdrawn. Overprotection tends to build up a schizoid personality and is an important factor in the etiology of schizophrenia. When overprotection is indulgent in character he may feel stiffled with the overdose of love which may result in aggresive traits like authority rejection, commanding and bullying.

Causes of Overprotection—These may be best stated by quoting Levy[3]:

"1. Long period of anticipation and frustration during which the woman's desires for a child were thwarted by sterility, miscarriages, or the deaths of infants.
2. Conditions in the child that expose him to a greater hazard for survival than other children; physical handicaps; illness.
3. Sexual incompatibility with the husband.
4. The loss of a mate.
5. Social isolation, lack of social contacts, lack of common interests between husband and wife.
6. Emotional impoverishment in early life—unhappy childhood, particularly, from the piont of view of libidinal satisfaction.
7. The development of dominating characteristics through the assumption of undue responsibility in childhood and the continuance of this role in marriage.
8. Thwarted ambitions.
9. Some parents have purposefully adopted the plan of giving their children a large amount of freedom as a protest against their own strict upbringing."

To these may be added other causes peculiar to Indian families. Overfondling of a child who is supposed to have brought good luck to the family; for instance, the birth of the child coincided with or was followed by an increase in the family income. There was another instance of spoiling a child because he was the only son in a family of five married brothers who, among them, had eight daughters and only one son Quite often, overprotection may be an overcompensation for an unconscious feeling of guilt over a fundamental rejection of the child.

REJECTION

The rejection of a child may sometimes be openly shown by the parents but is more often disguised. It may be shown by behaviour such as parents seing nothing in the child but his shortcomings. They do not provide the child with toys, his education is neglected, and they punish him for the slightest offence. The child may be put in an institution or in a reformatory or a boarding school not because circumstances demand taking such a step, but because the parents do not want to be bothered by the responsibility of bringing up the child. No time is spent by them in the company of the child, except to ask him, because they think it is their duty, whether he has done his lessons or not. Unnecessary and unfavourable comparisons with siblings or a neighbour's children is another indication of rejection.

The causes of rejection are many—The child may not be wanted for reasons of poverty or because there are too many children. The child may be defective either physically or mentally. The mother was very averse to further pregnancies, actually contraception was tried or abortion was attempted, but she conceived against her desire. There may be rejection by the parents because the child is a step-child or an adopted child or an illegitimate child. Hostility to a child may be due to a direct transference of the unconscious hostility to a parent of the same sex as the child.

Results of rejection—In the vast majority of delinquent children rejection by the parents is one of the outstanding causative factors. Rejection, when manifested by overstrictness or punishment and cruelty, produces in the child a hostility towards such a parent. This hostility then spreads to anything that stands for power or authority. He rebels against authority in general. To escape punishment from his father he starts lying. He plays truant from home and wanders. He may associate with companions like himself and become a member of a gang. He may take to gambling and may commit sex offences. Stealing may occur as a result of the influence of the gang. Very often the stolen article, particularly if it belongs to the rejecting parent, stands (in the unconscious mind) for the love he craves from that parent. Another unconscious motivation of stealing may be to get even with or to spite the father by bringing a slur on the family name. At school also he may have difficulty in adjustment. He rebels against the teacher (who is a parent substitute) and disobeys him.

The results of rejection may best be summed up as follows:

"........Affection for a child in his own or a substitute home is fortunately so general that its immense biological role in development may be overlooked, much as the need for oxygen might be overlooked by the uninformed who had never seen or experienced suffocation. Rebuke or punishment does not of itself provide a motive for the child. It only underlines the withdrawal of approval. The strict but loveless home may produce a severe delinquent.

This primary need of the child (need for stable and secure affection) cannot well be overemphasized. The moral aspect is also implicit in that the child will adopt the values of those whom it loves, admires and desires to emulate, and rebel against the code of those who owe but deny it affection. Thus a child may be emotionally stable and well adapted to parents who are themselves antisocial in outlook and so become a delinquent."[2]

PUNISHMENT

Punishment is still considered by a number of parents and teachers alike as a panacea for the behaviour problems of children both at home and at school. It is common experience in a child guidance clinic to hear parents saying that every method of "correcting' the child has been tried, not failing to add that punishment has also been tried but unsuccessfully. Nothing is more detrimental to the psychological development of the child than the evils resulting from punishment, particularly corporal punishment. In order to avoid it the child may resort to deceit and lying. It deepens the child's sense of inadequacy and the feeling of inferiority, particularly if the punishment appears to the child to be unreasonable, unfair and unjustly severe. If often resorted to, it causes in the child a feeling of rejection and hostility. Ultimately he may rebel and take to antisocial activities.

Corporal punishment should have no place in the 'treatment' of behaviour disorders and should be condemned. Infliction of pain in some of the erotogenic zones may be accompanied by a certain amount of pleasurable feeling, and frequent repetition of this pleasurable feeling may cause a desire for it to become fixed. Later on this desire may lead to a sexual perversion called masochism. Corporal punishment must be avoided. If it has to be used, let it be used sparingly and as a last resort with a full explanation as to why it is used. Punishment must be explicable to the child, fitting to the fault, short and to the point. It is high time that this age-old remedy for 'correcting' the child becomes obsolete.

PARTIALITY, FAVOURITISM AND UNNECESSARY COMPARISONS

The results of unequal treatment of siblings are evident. It tends to foster a spirit of unhealthy rivalry, jealousy and hatred in the mind of the child who is the victim of this attitude. The child may feel rejected and unwanted. He may feel that he is not coming up to the expectations of his parents which may increase his feelings of inferiority. Not only the parent but the sibling with whom he has been compared unfavourably becomes the object of his hostility. It makes adjustment at home and at school extremely difficult. Unnecessary comparisons are odious and should never be made in the presence of others.

FEEDING OF CHILDREN

Some mothers have a very neurotic attitude regarding the feeding of children. They believe that the child should never miss a meal and must eat a certain quantity of food in order that he may develop into a physically healthy child. Constant nagging about food is harmful. No greater disservice can be done to the child's health than coercing him to eat more in the hope of making him fat. He learns that if more fuss is made, more attention and sympathy are obtained by not eating, than by eating. Food fads or refusing to eat and sulking at the time of meals become weapons to seek more and more attention and dominate the household Missing a meal has never killed a child. His sulking should be ignored. If he refuses to eat he should be told that his dish would be kept for him for some time, say half an hour or so, after which it would be taken away and he would not get food till the next meal. If this procedure is strictly followed the habit of refusing food or sulking at meal time very often disappears.

QUARRELS BETWEEN PARENTS

Discord between the parents resulting from frequent quarrels between them is one of the common causes of juvenile delinquency. One of the most fundamental needs of the child, viz. need for security, can only be satisfied if the child feels that both his parents love him. He may take the side of one parent and start hating the other. Such a state of affairs is bound to lead to obstacles in the smooth development of the child's personality.

INCONSISTENT DISCIPLINE

Very often parents punish a child for a certain piece of mischief but at other times when they are in a good humour, not only do they overlook this mischief but may even applaud it. The child fails to understand whether that particular act of mischief is looked upon with favour or disfavour. Often parents openly disagree regarding the methods of upbringing of the child. This leads to emotional insecurity in the child. The parents should discuss their differences privately in the absence of the child. They should present a united front regarding the mode of upbringing of the child.

NEUROTIC ATTITUDE OF GRANDPARENTS

Inconsistent discipline is most likely to occur when parents and grand-parents openly differ in their attitude to the child. The child's training suffers. He wonders whether his parents or his grand-parents are right. He may learn to obey his indulgent grandparents and disobey his parents or vice versa. In some instances, taking advantage of the situation he learns to play off the generation against the other.

CONCLUSION

The conclusion may best be quoted in Leo Kanner's[1] own words:

"If, as we have seen strained relations between members of the family may, directly or indirectly, so affect a child as to create personality disorders, it is obvious that the specific form of association between the parents and the child himself must be of particular significance in the formation of his character and habits. It is especially the managements of his domestic socialization and the preparation for faultless communal adjustment that may seriously deviate from sound and sane standards. Most parents do their job well, with the use of common sense and the knowledge that child must be given a chance to grow into healthy manhood and womanhood, to receive protection when and where it is needed, to be fed and clothed and educated properly, and to develop responsibilities of his own in due time........"[1]

REFERENCES.

1. Kanner L. "Child Psychiatry" Pg. 92-93, Illinois, U.S.A., 1947.
2. "Mental Health" Vol. 10, No. 1, 1950 (Quoted from the memorandum issued by the Royal Medico-psychological Association on Juvenile Delinquency).
3. Symonds P. M.: "Psychology of Parent-child Relationships," Appleton Century, New York, 1939.

THE ANNUAL CONFERENCE OF THE ASSOCIATION OF PHYSICIANS OF INDIA

Impressions of a Correspondent

The Sixth Annual Conference of the Association of Physicians of India was held in the Medical College in the historic city of Amritsar on the 2nd, 3rd and 4th March, 1951.

One could get an excellent view of the Golden Temple surrounded by the Lake and the Golden Towers from the air which was more impressive, than when seen from the ground; that alone is worth the pilgrimage to the city.

Amritsar has been playing a considerable part in the struggle for freedom of India. The tragedy of Jallianwalla Bagh has been known to all Indians for the last 22 years. But since 1946, the people of Amritsar, by their sacrifice and suffering, have realised the value of freedom which people in other parts of India have not. The main streets of Amritsar have been shattered and destroyed by fire and communal riots just before the partition of the country and today, one only gets an insignificant idea of the destruction of the property in this historic city.

In such a place, the medical profession had organised to invite the annual celeberation of the Association. All practitioners and teachers, whether general practitioners or teachers in anatomy, pathology or surgery, contributed their share towards the success of the meeting. One and all were very hospitable. Students and doctors went out of their way to make the delegates comfortable and house them comfortably in their own houses, in the best hotels of Amritsar and the best places available, like the Circuit House. The delegates were spared all expenses. Not only did the doctors of the town show interest in the delegates but also the City Fathers who organised a very pleasant function in a specially erected colourful shamyana in the beautiful gardens of Rambag to welcome the delegates. The President of the Municipality, in welcoming the delegates, gave the history of the town and the part played by it in the struggle for freedom and in the trade of the country. His speech was delivered in beautiful flowery Hindi. The Textile Manufacturers' Association also gave a supper party to the delegates, showing that even trade was interested in the affairs of the medical profession of the city.

The social side of the Conference was nicely arranged and organised by the medical profession. The delegates were entertained with sumptuous meals at private houses and at a banquet in the Medical College Hall to which all the luminaries of the town were invited. The toast of the association was proposed by Dr. A. N. Goyle, Principal of the Medical College and Chairman of the Reception Committee. The Chief Minister, Dr. Gopichand Bhargava, who was unable to come to the opening session, made it a point to be present at the lunch and to address the Conference regarding the work done by his government towards improving the health of the people of the Province. The Indian Medical Association of the town welcomed the delegates to a tea party in its Hall on the first day of the meeting. Even though a surplus province, they had restrictions on serving cereals at all these parties. However, non-rationed articles were available in such plentiful quantities that it gave some idea of the rich high protein nutritious diet consumed by this martial province of India.

Individually and collectively, the medical profession had organised sight-seeing and visits to the hospital; also visits to the border between India and Pakistan. Even though some of the members were housed at different places far apart from each other, private transport was available to each of the delegates at any time of the day and night. Local organisers were always willing to undergo any inconvenience to themselves. The Medical Fraternity of Amritsar should be congratulated for such excellent arrangements both on the social and scientific side for the meeting of the Association.

The organisers had taken advantage of the presence of a number of all India doctors to arrange addresses by them to the local medical students.

The proceedings of the conference were conducted admirably by the able President Dr. P. Kutumbiah, Principal and Professor of Medicine, Christian Medical College, Vellore, who impressed the Conference by his simplicity, efficiency and oratory. His presidential address was full of the things needed for the advancement of medical science in this country. His speeches at various social functions were to the point and adequate replies on each occasion and everyone was happy at the choice of the person for the high office of the Presidentship of the Association.

The members of the Association had long informal meetings in order to find ways and means of improving the affairs of the Association, and they were satisfied with the new suggestions to be adopted by the Association.

On the scientific side, the Conference had a successful session, and twenty-three papers were read in three days, out of which ten instructive papers were contributed by the local members of the profession. One or two of the twenty-three papers read were most disappointing but one has to put up with them with a view to encourage members of the Association to contribute to the advancement of medicine. As usual in India, there were some last minute cancellations.

In the symposium of anaemias, Miss Chaudhuri (New Delhi) reviewed the work done by her during the last three years on anaemias in women. J. C. Patel (Bombay) drew analogy between Addisonian Pernicious Anaemia and Tropical Macrocytic Anaemia, and considered that aetiology in Tropical Macrocytic Anaemia might be due to deficiency of protein along with deficiency of absorption of various factors like folic acid and vitamin B_{12}, but besides the quantitative and qualitative deficiency there should be very little difference. Chhuttani (Amritsar) had collected a large number of cases of Koilonychia and worked out its incidence. He also pointed out that subacute combined degeneration was not uncommon. B. B. Bhatia *(Lucknow) still considered toxins as an aetiological factor in anaemia* of Ankylostomiasis. K. N. Gour (Agra) reviewed cases of anaemia with gastrointestinal symptoms during the last 5 years. S. S. Ugrankar (Bombay) narrated the part played by liver, folic acid and vitamin B_{12} in the treatment of anaemia. M. L. Pathak (Amritsar) told the audience his experiences of blood transfusion in anaemias. Gurbuxsh Singh (Amritsar) and K. S. Mathur (Agra) gave their experiences with intravenous iron in hypochromic anaemias. G. Coelho (Bombay) gave the incidence of rheumatic fever in children in Bombay, while R. P. Malhotra (Amritsar) analysed 200 cases of coronary thrombosis. Singh (Orthopedic surgeon, Amritsar), viewed 70 cases of Sciatica from a physicians angle. K. L. Wig (Amritsar), M. L. Aggarwal (Amritsar) and S. Sen (Delhi) reviewed lung suppuration from medical, radiological and therapeutic side. A little higher level of discussion following the papers is desirable.

On the whole, the Conference was a success. The invitation of Dr. Bankat Chandra of Hyderabad to hold the next Conference at Hyderabad was accepted by the Association.

MEDICINE

THE TREATMENT OF ULCERATIVE COLITIS, Beaumont, G. E.: B.M.J. 2: 937-939, 1950.

The treatment of ulcerative colitis being varied the author has put forward two illustrative cases and has outlined the treatment he follows. In case 1, a married woman aged 31 years was admitted to hospital with a history of recurrent attacks of diarrhoea containing blood and mucus and occurring more at night, for the last two years. The stools were accompanied by severe griping abdominal pains. She looked ill, was pale, and thing and had lost over 2 stones in weight, Examination showed that the mucous membrances were very pale, the teeth carious and the blood pressure 100|70 mm. Hg. Her temperature was raised to about 102 deg. F in the evening, falling to 99 deg. or 100 deg. F in the morning. The abdomen was distended with gas and the transverse and descending colon were palpable. The bowels were opened on an average of six times by day and six times by night. The agglutination tests were negative to typhoid, paratyphoid, dysentry and paradysentry groups of organisms. The stools only showed pus cells, red corpuscles and macrophages. On culture only Bact. coli types of organisms were grown. The blood examination showed a severe hypochromic anaemia. Sigmoidoscopic examination showed numerous bleeding ulcers about 5 in. from the anus. In the treatment of such cases as these, the author recommends a blood transfusion to raise the blood count to normal, to restore the plasma albumin and to effect an adequate mineral concentration in the blood. This case received three pints of blood. The patient was given ½ gr. of phenobarbitone three times a day to calm her, and 1|200 gr. of atropine sulphate in water by mouth three times a day to cut down vagal and sacro-pelvic parasympathetic nervous impulses to the colon. Bismuth and kaolin preparations must not be given, as they may cause caking of the intestinal contents and pressure necrosis of the intestine. For the severe abdominal pain, 15 mm. of Tn. opium in water was given. Within 10 days the patient felt much better. The stools were three in number in 24 hours. The temperature however was still raised in the evenings. In addition to the above treatment the patient was given sulphaguanidine 1 G. every six hours for two weeks, vitamin B complex two capsules daily and 4 ml. of hepastab intramuscularly every 4 days. The diet recommended was of high protein, high caloric and low residue one. After two months there was no diarrhoea, no blood in the motions, no abdominal pain, but also no gain in weight. A month after this, she had a relapse of the condition, but not of the same degree as before. A blood transfusion of 2 pints was given and she felt better, had good appetite and was gaining weight at the rate of 3½ lbs a week. After another 9 months she had another relapse. A blood transfusion was given again and in addition to this phthalyl-sulphathiazole 1 G. 3 times a day for 2 weeks was given orally and transentin. 75 mg. tablets 1 or 2 a day for the abdominal pain. After this treatment the patient felt much better and has no complaints since.

In the second case, the author was asked to see a married man aged 45 years, suffering from the same complaint, in whom the nervous or psychological symptoms were more in evidence. This patient was worried about his financial commitments and often had digestive troubles with diarrhoea whenever he was over worked. Blood examination showed a moderate degree of hypochromic anaemia, the stools contained mucus and blood, but no abnormal organisms were found on culture. The corrected sedimentation rate was 18 mm. at the end of one hour. The temperature was normal. This did not appear to be a very severe case of ulcerative colitis, and the psychological factor was a much more prominent feature than in the case previously described. The patient was given a course of phthalyl-sulphathiazole 1 Gm. 3 times a day for 14 days together with a high caloric, high protein diet, 200 mg. of ascorbic acid daily and 6 gr. tablets of ferrous sulphate thrice daily. In 15 days the stools were controlled and in a month's time the patient was discharged and sent home in a good condition—having gained 2 lbs and passing one stool in 24 hours with a little mucus, but no blood. In this case no transfusion was given as the anaemia was not severe.

The cause of ulcerative colitis being unknown, treatment must be symptomatic, and repeated transfusions are of the greatest value. The ultimate results, however, are very unsatisfactory.

Eric Coelho.

BRONCHIETASIS, Lander, F. P. L.: B. M. J. 2: 1486-1488, 1950.

Aetiology—The most common causes of bronchiectasis are the respiratory disorders of childhood. First and foremost is whooping cough, followed by measles with its attendant bronchopneumonia, primary lung tuberculosis, bronchitis and asthma and inspired foreign bodies including debris from nasal and oral infections, in that order of frequency. In adults, past diphtheria claims a few cases. Pulmonary tuberculosis plays an important role as life advances. In middle and later life, bronchial carcinoma claims a large number of cases.

Symptoms and signs—Many cases are completely symptomless. Those that produce symptoms come with a very characteristic history of recurrent attacks of respiratory disease. Bronchitis, pneumonia and pleurisy recur and recur, and in the intervals between they have chronic cough with copious purulent sputum which may disappear in the summer or during dry weather. Occasionally slight haemoptysis may occur. When the infection is more virulent, the child may be stunted and if a large portion of the lung is involved, dyspnoea may be a prominent feature. As adult life is attained, the acute episodes become less frequent but without amelioration of cough and sputum. Dyspnoea becomes more pronounced now, and is often distressing. Occasionally haemoptysis may be large. In a few cases, haemoptysis at infrequent intervals may be the only complaint. In bronchiectasis, signs may show only an area of diminished breath sounds to suggest that emphysema is making the deeper lying dilated bronchi, or signs may be of lobar distribution, with dullness on percussion, and either absent breath sounds or loud bronchial breathing or rales in the suspected area. Displacement of the heart to the affected side is present in unilateral cases. When the upper lobe is at fault, deviation of the trachea to the affected lobe is found. Clubbing of the fingers is a variable finding and depends on the extent to which the lung is involved rather than the degree of dilation or the intensity of infection. Bronchiectasis is most common in the lower lobe. The involvement of isolated segments of the lungs also occurs frequently. Radiological appearance:— The ultimate diagnosis of bronchiectasis depends on the display of dilated bronchi outlined by a radio-opaque oil but the diagnosis can be made with some degree of certainity from a plain roentgenogram. The roentgenographic changes are of two main varieties (1) atelectasis and (2) compensatory mechanisms which attend collapse: localized emphysema displacement of the mediastinum, and distortion of the diaphragm. The dilated bronchi themselves throw no shadow. At times the dilated bronchioles and alveoli have a "soap-bubble" appearance.

Treatment—The treatment is aimed at eradication of the infection in the dilated bronchi and this is accomplished by postural drainage of the patient at frequent intervals so as to empty his bronchi, and by giving him a specific drug against the organism detected in his sputum. The posture of the patient depends on the bronchi which are affected. If they are anterior to the bifurcation of the trachea, the patient should lie on his back on a bed with the foot raised 6 to 9 inches from the ground. If the left lung is affected, he should lie partly on his right side, if the right lung is involved, he should lie partly on his left. If the affected bronchi is posterior to the bifurcation of the trachea the patient must lie on his face on the affected side. At first, sleeping all night in this position is necessary; during the day, more drastic postures like hanging over the edge of the bed with the head vertically down, should be adopted. The best results are obtained with combined postural and penicillin treatment. Half a million units of procaine penicillin should be injected intramuscularly for 14 days in those individuals where sputum showed penicillin sensitive organisms. In those cases where there are a preponderance of gram negative organisms combined streptomycin (1 G. a day) and penicillin should be given. In those cases where there is a large amount of sputum and widespread disease, penicillin by inhalation may also be resorted to. The inhalation can be given by means of a Collinson inhaler or by atomizers, the amount given by inhalation being 1 lac units in 5 ml. repeated 3 to 4 times a day. With advances in surgical technique in recent years, lobectomy and pneumonectomy are safe procedures. The mortality from these operations is less than the overall mortality from bronchiectasis. For this reason many physicians and surgeons advocate operative treatment in all cases of bronchiectasis. This should not be the rule unless the patient has had the full benefit of a course of postural drainage and penicillin treatment, nor should operation be advised for at least a year after the presence of a bronchiectatic condition has been first demonstrated.

Complications—The commonest complaint is chronic bronchitis. Tuberculosis occurs not infrequently. Cerebral abscess is a complication in the more severely infected cases. Amyloid disease is a very rare complication.

Prognosis— The outlook for uninfected cases of bronchiectasis is good Such patients, can marry, have children and live to a ripe old age; there is a likelihood of a second infection but with the advent of the antibiotics this complication is not serious. Where the infection is virulent, death may result in a few months after the onset or during a succeeding lung infection but antibiotics will come to the rescue and render the case suitable for surgery. Where the disease is widespread, beyond the scope of surgery and cannot be controlled by antibiotics, the outcome is poor. These cases however are rare. During the first year of the disease there is always the possibility of re-expansion of the lung and that the infection may die out with consequent disappearance of bronchiectasis.

Eric Coelho.

ORALLY ADMINISTERED ANTIBIOTICS AND THE VENEREAL DISEASES, Willcox, R.R.: Nature, 166:466-468, 1950. 1 table, 27 references.

The author, a famous venereologist, reviews the use of four potent antibiotics—Penicillin, Streptomycin, Aureomycin, Chloramphenicol—in venereal diseases. Among them, they cure all the venereal diseases.

Streptomycin is ineffective when given by mouth. However, oral penicillin is sometimes used.

Chancroid: He considers sulphonamides the first choice. Streptomycin should be used for sulphonamide-resistant cases; Aureomycin for streptomycin-resistant cases.

Gonorrhea: Penicillin is a drug of choice but a follow-up for 6 months is necessary for detecting mixed syphilis. The U.S. Navy has used oral penicillin tablets in the dosage of 250,000 units as a prophylactic. All the three antibiotics given orally are capable of curing gonorrhea.

Granuloma Inguinale: Streptomycin is the drug of choice. Aureomycin and chloramphenicol may be used to reinforce the action.

Lymphogranuloma venereum: Sulphonamides take first preference. Other antibiotics may have doubtful effect. Penicillin given parenterally is the most effective of the antibiotics.

Non-specific Urethritis: Sulphonamides and streptomycin share equal honours in the treatment of this condition. Aureomycin and chloramphenicol may have some action.

Syphilis: Aureomycin and chloramphenicol have some action on the Treponema pallidum but are inferior to parenteral penicillin. Oral penicillin will be required in extravagant doses and is too risky for a serious disease like syphilis, but may be employed for weak babies with congenital syphilis. The author has given a table of the drugs of choice for different venereal diseases which is reproduced below:

Disease	First	Second
Chancroid	Sulphonamides	Streptomycin
Gonorrhea	Systemic Penicillin	Streptomycin
Granuloma inguinale	Streptomycin	Systemic penicillin
Lymphogranuloma venereum	Streptomycin	Aureomycin
	Sulphonamides	Aureomycin
Non-specific urethritis	Streptomycin	Aureomycin
Syphilis	Systemic penicillin	More penicillin

Oral antibiotics are second choice drugs, but they can have a prophylactic value.

J. C. Patel.

SURGERY

THE REPLACEMENT OF BLOOD VESSELS BY POLYTHENE TUBES,

Moome, H. D.: Surg. Gynac. Obstet. 91: 591-600, 1950. 5 figures, 2 tables, 16 references.

The author reviews the methods used to replace damaged blood vessels and the unsatisfactory nature of the results stimulated the experimental study of the problem.

Tuffier and Magins had used paraffin buried silver tubes, Murray and James used glass tubes with large doses of heparin, with poor results. Blakemore and associates used vitallium tubes in 15 dogs with one success where the tube remained patent for 5 days. Vein grafts have been found more successful.

De Bakey and Simeone and Mustard mention the use of plastic tubes in man Hufnagel used perspex tubes with success in dogs and Donovan described the use of polythene tubes in dogs. The author describes the use of polythene tubes to replace lengths of the thoracie aorta in 20 rabbits Tubes were of 2.5—3 mm. internal diameter except in 2 rabbits where 4 mm. diameter tubes were used. The rabbits were anaesthetised with pentobarbitone and artificial respiration with a small physiological pump effected by means of an endo-tracheal tube. The aorta was cut completely except in the earliest experiments where it was only partially divided. The polythene tube 14—26 mm. long was introduced with care not to push up the intima and secured by ligatures at both ends. No anti-coagulants were used. Arteriograms were taken to establish patency. Some were killed at varying intervals to note the condition of the tube and 4 were alive and well 3½ to 10½ months after operation. In postmortem findings the tube seemed normal in all respects even in those where a thrombus had formed at the junction of tube and aorta. A strong capsule around the tube firmly attached it above and below and appeared within a few days. Microscopically the layers of aorta ceased abruptly between the sutures to be replaced by dense collagenous tissue about the same thickness or in some places thicker than the original wall and in these cases at the end there was the beginning of endothelial lining inside the tube. The same method was used to replace lengths of the internal jugular vein but in all 6 animals clotting had occurred by the time a venogram was taken.

Eustace J. De Souza

INTUSSUSCEPTION IN CHILDREN—ITS DIAGNOSIS AND TREATMENT,

Nordentoff, Jens Munck: Overseas Postgraduate Med. J. 5: 76-86, 1950.

The author in evaluating the conservative operative methods of treatment traces the history of the barium enema method and why it was abandoned in some countries and why apparently revived in others.

In stressing the radiological diagnosis, the straight film in recumbent position is used to estimate the gas distension and also whether large or small bowel is involved. The diagnostic barium enema is given, if not contraindicated by a possibility of appendicitis. The "intussusception figure" is likened to a "fork|figure," and is the commonest form. If the barium has advanced for some distance above the intussusceptum a negative picture of the latter in the form of a filling defect will be seen. If the intussusception consists of small bowel broad lines of barium shadow may demonstrate that the intussusception is one that has passed through the ilio-caecal junction (Edberg's sign). Pure colic intussusception may be diagnosed from the straight film and with barium the distance from the funnel shaped termination of the jar figure to the cup shaped caput indicates the length of the intussusception. Pure ilieal intussuception is recognised if the enema flows into the small bowl. Entero-colic intussusceptions constitute 80 per cent of cases and Edberg's sign is positive.

The diagnosis and treatment by barium enema go hand in hand. The diagnostic infection being made under low pressure and treatment followed by allowing the fluid to flow under a pressure of 3-4 feet. In cases of less than 24 hours duration even 4-6 feet may be used but never more than 6 feet. Complete filling of the caecum and satisfactory reflux into the ileum are two important radiological signs of reduction. The dangers lie in the risk of thinking the reduction is complete when in fact it is not.

The author however points out that intussusception still comes under the care of the surgeon who refers the case primarily for reduction by the opaque enema method and if this fails or if reduction is uncertain operation is necessary.

Eustace J. De Souza

SURGICAL CONSIDERATIONS IN THE TREATMENT OF BRONCHIECTASIS, Vest, James C.: Surg. Clin. Nr. Am.: 1299-1313, 1950.

The author reviews the various therapeutic approaches to the problem from the early non-surgical methods to the most modern advances in technique where the intra-hilar individual ligation and segmental resection operations have been developed and generally accepted. The onset of symptoms due to bronchiectasis are seldom recognised as such, and are often referred to an episode of pneumonia, whooping cough, broncho-pneumonia or measles. In some there is cough with increasing frequency and quantities of sputum, foul and purulent, and at times containing blood. Chiefly a disease of the young it is rarely congenital, and in more than fifty per cent of cases, bilateral, the lower lobes being most often affected. The majority of cases can be suspected by a complete history and physical examination. Chest X-Rays and fluoroscopy supplemented by bronchography can demonstrate the involved bronchi in all cases. Careful technique is essential in this last procedure. Bronchoscopy should not be omitted, lest foreign bodies, bronchial stenosis or a new growth be missed. Also it is valuable for the removal of secretions prior to bronchography. When diagnosis is established only resection of the affected tissue is curative.

In aged patients or where extensive disease precludes definitive treatment palliation and prophylaxis against recurrent pneumonitis is effected by combined, antibiotic therapy, postural drainage and bronchoscopic aspiration. While children do better, age does not preclude operation but here considerations of extensive concomitant disease, are important considerations. While surgery is indicated in disease of one lung, one lobe, one segment of a lobe or combinations of lobes, bilateral affection presents a problem. However the increased mortality and morbidity of the disease justifies radical treatment. Though most cases require lobectomy, in restricted disease, segmental resection is a refinement of technique the evaluation of which is still to come, but even now, finds enthusiastic support.

In the preoperative course, besides the careful general preparation of the patient, the elimination of tracheo-bronchial contamination is the most important factor and proper antibiotic therapy, with penicillin both intramuscularly and by aerosol method, streptomycin and aureomycin have valuable effects. Drainage both postural and in some instances by bronchoscopic aspiration are valuable. The posterolateral approach with intra hilar individual identification and ligation technique is used routinely. Following removal of a lobe the hilar region and pleural cavity is irrigated and the sutured bronchus tested for any leak. The pleural cavity is drained by the waterseal method in the posterior department and high anterior areas, and these tubes kept functioning. Re-expansion is verified by immediate post-operative X-Ray, and is facilitated by bronchoscopic aspiration. Carbon-dioxide and oxygen inhalation are used every hour to stimulate respiration and penicillin and streptomycin given till the patient is afebrile for several days.

The previous dismal outlook has been completely changed, the author's results showing a mortality of approximately one per cent. In bilateral disease the risk however is greater but rapidly improving.

Eustace J. De Souza

METHOD FOR RELIEVING IRREDUCIBLE INTUSSUSCEPTION, Sawyer, K. C.: Am. J. Surg. 80: 871-872, 1950.

The author describes a simple manouvre which usually succeeds in reducing the terminal segment of an irreducible intussusception. After most of the intussusception has been reduced one often finds that the last portion refuses to reduce, and in this case a resection or some other drastic procedure has to be attempted. The authors method often succeeds at this stage.

The method consists of two manouvres. First, after the last stage of reduction is reached and an irreducible condition found, the thumb and forefinger of the operating hand are inserted into opposite sides of the ileocaecal valve, and gentle pressure exerted. This pressure is gradually increased in such a manner as to produce a gradual relaxation of the valve with a resulting dilatation. It takes a little time, the pressure being continuous and increased gradually. At first the valve is felt as a very firm, cartilaginous like ring which is almost closed. If sufficient time is taken for this first manouvre, the ileocaecal valve gradually relaxes and opens sufficiently to permit the start of the second manouvre.

In this second manouvre the colon is gently grasped at a point just distant to the end of the intussusception, then gradually squeezed. This causes the ileum to return through the ileocaecal valve, and the manouvre is continued until complete reduction is obtained. Sometimes it is helpful to hold the intussuscepted ileum close to the ileocaecal valve in a position that will help to guide the return of the intussuscepted portion. This method is simple and very effective.

E. J. Borges.

USE OF OXIDISED CELLULOSE AND CORTISONE IN THE PREVENTION OF EXCESS BONE AND FIBROUS TISSUE FORMATION,

Stinchfield, F. E.: Journ. Bone and Jt. Surg. 32A: 739-749, 1950.

One of the chief factors interfering with a satisfactory end result in joint surgery is the limitation of motion postoperatively, due to excess of bone and fibrous tissue formation at or near the site of surgery. The authors describe the results of using oxidised cellulose and cortisone to prevent this complication.

Oxidised cellulose or absorbable gauze was originally used by Lattes and Franz in 1945. The material is cellulose which has been oxidised by the use of nitrogen dioxide. It becomes anhydroglucuronic acid which when inserted into the tissues produces a lowered pH. The material used is sterilised by formaldehyde. Experiments on dogs revealed its power of preventing bone formation when used locally. In one instance the oxidised cellulose was placed between the fragments of a fractured radius, and the fracture failed to unite. The cavity was lined by flattened cells making it resemble an adventitious bursa and here and there were minimal, if any, signs of bone repair.

To test the clinical application of oxidised cellulose the author has used it in twenty-two joint arthroplasties and in 20 cases such as removal of exostosis, myositis ossificans, fixation of radial heads etc. In all these cases the patients were comfortable after operation and the degree of motion was greater than that achieved without the use of oxidised cellulose. However, though bone formation was inhibited fibrous tissue formation progressed normally or at an accelerated rate. Therefore it was necessary to attempt some means of retarding the growth of fibrous tissue.

Experimental work by Ragan, Howes, and their associates has shown that wound healing is markedly inhibited by the administration or cortisone. There is decreased activity of mesenchymal tissues and decreased fibroblastic proliferation. Experiments on dogs were carried out to study the effect of cortisone on the end results of arthroplasties. Four types of experiments were carried out. First, as control, no cortisone was used. Second, the same type of arthroplasty was performed, but 25 mg. of cortisone were instilled in the joint. Three local instillations of 25 mg. were repeated at intervals of two days. Third, 25 mg. were instilled at operation, and daily for three weeks 10 mg.|kilogram was injected intramuscularly. Fourth, no local instillation was done but 10 mg.|kilograms were administered intramuscularly daily beginning two days prior to operation and continuing for three weeks.

All the animals were sacrificed 5 weeks after arthroplasty. In the control group (without cortisone) the gross hip specimens showed a great deal of crepitation, excess of fluid and markedly thickened capsule with about 30 per cent less mobility than the dogs given cortisone. The latter group showed no crepitation, very little clear joint fluid, no capsular thickening and good mobility and hardly any inflammatory reaction.

As a result of these experiments the authors have used cortisone in humans as follows: 100 mg. are injected in the traumatised joint or in arthroplasty joints at the time of the operation and the dose is repeated on the second fifth, tenth and fifteenth days after operation. On the seventh day when the skin wound has healed, 100 mg. of cortisone are given intramuscularly daily for three weeks. The results are very encouraging though sufficient time has not elapsed for a final evaluation of the valuable method of preventing joint stiffness.

E. J. Borges.

BREAST ABSCESS—A RESULT OF LACTATION FAILURE, Newton, M. and Newton, M. R.: Surg. Gynae. Obstet: 91: 651-655, 1950.

The development of a postpartum breast abscess may be best understood if it is regarded as a final stage in the failure of lactation. One of the difficulties of considering it as such stems from the fact that the case of a woman with this disease falls between the obstetrician, pediatrician and surgeon.

Three factors are usually mentioned as being important in the development of a breast abscess: trauma, infection and stasis. Recent work on the function of the let-down reflex in human lactation makes it possible to clarify and co-ordinate the part played by each of these factors. The "let-down reflex" is a mechanism, entirely distinct from the secretion of milk, by which the milk which is already in the breast, is expelled actively in response to the stimulation of sucking. This reflex is extremely sensitive to emotional stimuli and can be inhibited by pain, emotional upheaval or fear Inhibition causes stasis in the breast and creates one of the factors responsible for breast abscess. Cracks in the nipple resulting in pain may inhibit the reflex. Emotional factors are important. In Dundee, Scotland, Fulton reported an incidence of breast abscess of 8.9 per cent between September 1941 and December 1943—a period of grave war and bombing anxiety, whereas the normal incidence is about 0.1 per cent.

The use of stilboestrol does not necessarily prevent breast abscesses. Forty-one per cent of the 86 cases reported by the authors in this series had received stilboestrol some days before admission for abscess. The common infecting organism is the haemolytic staphylococcus aureus. It is unlikely that any of the commonly practised methods of nipple care keep the nipples free from bacteria, though there is some evidence that segregation of persons harbouring pathogenic organisms in the nasopharynx does diminish the incidence of infections of the breast.

Prevention of breast abscess should therefore be most concerned in preventing failure or lactation. A recent study of the relation of the mother's attitude to her ability to breast feed shows that only mothers who wholeheartedly desire to breast feed are likely to be successful. Mothers who express indifference to or dislike breast feeding usually secrete less milk, the let-down reflex functions less effectively in these. If we believe that breast milk is better for the average baby then we have the choice of trying to influence attitude during the period of pregnancy or of recognising the inevitable and not allowing the mother to try lactation. It is also essential to help the let-down reflex early in the puerperium by relieving nipple pain and avoiding discomfort, embarassment, emotional disturbances and distractions both in the hospital and at home.

E. J. Borges.

PEDIATRICS

DUODENAL ULCER IN INFANCY, Hollander, M. and Stark, M.: Pediatrics 6: 676-685, 1950.

Peptic ulcer in infants is a relatively rare condition. Since 1825, only 300 cases have been reported. Unlike adults, in infants it occurs equally in both sexes. It has been reported in every age group. Perforation of a gastric ulcer has been observed even in utero. Symptoms usually commence in the new-born period between the sixth to the tenth week. A few cases with clinical signs and symptoms may recover without confirmation by roentgenograms or operation.

The etiology of duoudenal ulcer in infancy is unknown. The authors review the various theories like external trauma, vascular, bacterial, chemical and neurogenic disorder, which have been invoked to explain the etiology. The role which psychosomatic factors play in infancy is undetermined, and hard to evaluate in new-born infants.

Peptic ulcer in infancy is a typical, and diagnosis usually overlooked. Haemorrhage is the only definite symptom pointing to duodenal ulcer. Haematemesis is less frequent than melaena, and may occur alone or with the latter. The loss of small amounts of blood may produce a serious state. Sometimes collapse so acute and so severe as to suggest perforation may occur. The possibility of perforation of an ulcer must be considered whenever there is sudden collapse in an infant. When this occurs, death usually ensues within 24 hours. Spasm of the pylorus, and less commonly pyloric stenosis may give rise to vomiting. Duodenal ulcer must be borne in mind when symptoms suggesting pyloric stenosis are seen for the first time in an infant over the age of 3 to 4 months. Roentgenographic studies may occasionally reveal the lesion though not so easily as in adults. Because of the danger of aspiration, lipiodol is recommended as a safer contrast agent than barium. Treatment is surgical, indications for operation being perforation, haemorrhage, pyloric stenosis and pylorospasm, with early blood transfusions to sustain the child prior to surgery.

The authors report a case admitted on the first occasion at the age of 6 weeks with a diagnosis of congenital hypertrophic pyloric stenosis for which a Fredet-Rammstedt operation was performed. The child improved temporarily, but was re-admitted when he was 9 weeks old. Roentgenograms did not reveal anything striking. Soon after admission he developed melaena and haematemesis and later signs of collapse. Despite treatment, the child died before any surgical aid could be administered. At autopsy a careful search did not reveal any sign of a duodenal ulcer, though suspected clinically. However, after a formalin fixation, an ulcer was found on the posterior surface of the duodenum close to the pyloric sphincter.

F. A. Nazareth.

ORAL PENICILLIN IN CHILDREN: Doxiadis, S. A., Emery, J. L., Stewart, S. M.: B. M. J.: 1: 16-18 1950. 1 table, 16 references.

Owing to the conflicting reports on the oral dose required and on the value of antacids, the authors felt that a study on these points was necessary before penicillin could be used by mouth for therapeutic purposes. Seventy-six children aged 2-15 years were given penicillin two or more hours after a light breakfast. It was in tablet form, each containing 200,000 units. The dose given varied from 1000 to 7000 units per lb. of body weight. Sodium citrate, 48 gr. in 1 oz of flavoured water was used as antacid and was given immediately before or after the penicillin. The blood and penicillin serum levels were estimated by Fleming's methods. The blood was taken before the penicillin was given and three hours later. In many children the blood was taken at varying intervals. A total of 208 test doses were given, involving 632 penicillin assays. The level of 0.06 units per cc. of serum was considered the minimum necessary for satisfactory therapy.

The authors obtained the following results. In those children who had no antacid, an adequate bacteriostatic level was obtained in 55 per cent of the cases that received penicillin in less than 4000 units per lb of body-weight, in 80 per cent of those who had taken between 4000 and 5,999 units per lb of body-weight and in 97 per cent of the cases that were given between 6000 and 6,999 units per lb of body weight. When an antacid was given together with the penicillin, 50 per cent. receiving 1000 to 1999 units per lb of body weight, 87 per cent receiving 2000 to 3999 units per lb of body weight and 95 per cent receiving 4000 to 5999 units per lb of body weight had a bacteriostatic level three hours after taking the penicillin tablet. From these results the authors came to the conclusion that for a reliable bacteriostatic level of 0.06 units per cc. three hours after the digestion, the single dose of penicillin should be not smaller than 6000 units per lb. of body weight—that is 48,000 units per lb. of body weight in 24 hours and that simultaneous administration of an antacid allowed a reduction of this dose by approximately 50 per cent.

Eric Coelho.

VENEREAL

TREATMENT OF GUYCHOMYCOSIS WITH AMMONIACAL SILVER NITRATE SOLUTION, Franks, A. G. and Sternberg, A.: Archives of Dermatology and Syphilology. 62: 287-289, 1950.

Guychomycosis, especially when due to **Trichophyton rubrum**, is a resistant condition and hence the authors tried a new treatment with complex silver salt in their 25 cases of fungus infections of nails and toes.

Of the total 25, 18 were found to be due to **Trichophyton rubrum** and 7 were due to **Candida albicans** (i.e. **Monilia albicans**). Clinical diagnosis was confirmed by culture on Sabouraud's or corn meal media.

Ammoniacal silver nitrate solution (P. L. Condit Co.) is a liquid of high purity with the following proportions: silver 29.50 to 30.5 per cent: ammonia 9.35 to 9.60 per cent (P.C.). Ratio of silver to ammonia was 3.10 to 1.0.

The solution was applied with a capillary pipette to affected nails in the clinic at weekly intervals. As originally suggested by Nickerson and White, prior to each treatment, the patient was instructed to clip and scrape the nails. Slight burning or stinging sensation may be complained of. Six to fifteen treatments with an average of ten were administered.

As for the results, 6 out of 18 cases due to **Trichophyton rubrum** had temporary improvement. In 7 cases due to **C. albicans** decided clinical improvement was noted in 5 and no improvement occurred in the remaining 2.

The authors attribute failure and success in **T. rubrum** cases and **C. albicans** cases to deep and superficial affection of the nails respectively. However Nickerson and White obtained good results even in **T. rubrum** cases as well.

T. K. MEHTA.

Indian Journal of Medical Sciences
(INCORPORATING THE MEDICAL BULLETIN)

VOLUME 5 MAY 1951 NUMBER 5

COPYRIGHT BY THE INDIAN JOURNAL OF MEDICAL SCIENCES

CARDIAC CIRRHOSIS †

K. S. Mathur,* and P. N. Wahi*

Since the days of Bacqueral[2] (1840), it has been debated whether cirrhosis of the liver is ever the outcome of long standing congestion of that organ due to heart failure.

Pick[21] in 1896 described three cases, which he called pseudocirrhosis of the liver resulting from chronic adhesive pericarditis. This was deceptively similar to one of the mixed forms of hepatic cirrhosis with enlargement of the liver and considerable ascites but no jaundice. In his opinion this was caused by disturbances of the circulation of the liver due to latent pericarditis. These circulatory disturbances led to an increase in the connective tissue (fibrosis or cirrhosis) which in turn caused stasis in the portal circulation with ascites.

Ophuls,[20] in a statistical survey of 3000 autopsies came across 22 cases of cardiac cirrhosis. Menne and Johnston[18] reported 17 cases of congestive cirrhosis among 6500 autopsies but did not include them in the category of true cirrhosis. Boles and Clark[4] found 33 cases of cardiac cirrhosis among 4000 autopsies, this form being second in frequency to the Laennec type. Boland and Willius[3] accepted the diagnosis of cirrhosis in 5 of the 75 cases of heart disease with either a prolonged single or multiple episodes of congestive failure.

Katzid, Waller[8] and Blumgart[10] found that in 286 cases where death was due to heart failure, the incidence of hepatic fibrosis was three times as great as in 1714 control autopsies. The incidence and severity of the fibrosis of liver increased with the duration of the right heart failure. Garvin[7] investigating the findings in 6548 consecutive postmortem examinations done at Cleveland City Hospital, found that 790 of these had died of heart disease. 35 of these 790 cases (4.4 per cent) showed evidence of cirrhosis of liver. This was found mostly in those who had either chronic or recurrent congestive failure secondary to rheumatic heart disease (14 of 119 cases) or to hypertensive heart disease (14 of 264 cases).

---

† Presented at the First Annual Meeting of the Indian Association of Pathologists at Agra.

* From the Departments of Medicine and Pathology, S. N. Medical College, Agra.

Among the 4200 consecutive autopsies reviewed by Kolestsky and Barnebee[12] there were 164 cases of cirrhosis of the liver (4 per cent). Of these, 74 cases were of Laennec's cirrhosis, 31 cases of obstructive biliary cirrhosis, 30 cases of congestive or cardiac cirrhosis and 15 of toxic cirrhosis. The congestive lesions comprised 18 per cent of the cirrhotic livers and occurred in 0.7 per cent of the total number of autopsies. The cardiac cirrhosis occurred essentially in patients with rheumatic heart disease (15 cases) less frequently in hypertensive patients (5 cases) and rarely in other etiological forms of heart disease except chronic constrictive pericarditis. Ascites and splenomegaly were not uncommon associates.

TABLE I *Showing the incidence of Cardiac Cirrhosis in various types of heart diseases,*

Type of Heart Disease	Number of cases of Cardiac Cirrhosis	
	Garvin[7] 35 cases	Kolestsky & Barnbee[12] 30 cases
Rheumatic Valvular Disease	.. 14	15
Hypertensive Heart Disease	.. 14	5
Coronary Heart Disease	.. 3	1
Cor Pulmonale	.. 1	1
Chronic Constrictive Pericarditis	.. 2	5
Syphilitic Heart Disease	.. 1	0
Arteriosclerotic Heart Disease	.. 0	1
Congenital Heart Disease	.. 0	1
Unknown Etiology	.. 0	1

In the experience of White,[26] cardiac cirrhosis is uncommon. The more definite cases have been those with congestive failure due to mitral stenosis, with or without tricuspid stenosis, and chronic constrictive pericarditis. He emphasised that the liver may be engorged with blood and ascites may be present in such cases for a long time before any appreciable cirrhosis of the liver develops. In other cases after years of hepatic congestion, liver atrophy is found along with areas of regeneration, and finally a real cirrhosis may develop with ascites *out of proportion to the degree of dependent oedema.*

A review of over 7000 autopsies performed at the Los Angeles County General Hospital during 1942-46, was undertaken in 1950 in a clinico-pathological study of cardiac cirrhosis by Kotin and Hall[13] who found 66 cases of cardiac cirrhosis among 600 cases of decompensation. Recurrent bouts of decompensation seemed to be most effective in producing hepatic fibrosis. The degree of fibrosis was taken as the criterion for classifying them in four groups.

Wahi and Mathur[24] did not find any case of fully developed cardiac cirrhosis in their study of histological changes of the liver in congestive failure. This was attributed partly to the small number of cases and partly to the short duration of illness of the cases studied in that series. Lambert[11] and Allison, and Menne and Johnston[18] had reported the lesions non-existent.

The purpose of this study is to determine the frequency and nature of cardiac cirrhosis from a critical analysis of the clinical data in 690 cases of congestive heart failure and the histological studies on liver tissue specimens obtained from 61 of these cases either by needle biopsy or at autopsy.

MATERIAL AND METHODS

The clinical data for this study has been provided from an analysis of 690 cases of congestive heart failure admitted to the Sarojini Naidu Hospital, Agra, between January 1st, 1941 and December 31st, 1948. The duration of heart failure, the number of attacks of cardiac decompensation, the clinical palpability of liver and spleen, and the presence of ascites and jaundice were studied in all these cases. These cases have been classified as follows according to their etiology:—

TABLE II—*Etiological classification of cases of congestive heart failure.*

Etiology of cardiac decompensation	Number of cases studied.
Rheumatic Endocarditis	.. 234
Cor Pulmonale	.. 222
Hypertensive and Coronary Heart Disease	.. 142
Syphilitic Heart Disease	.. 6
Subacute Bacterial Endocarditis	.. 6
Congenital Heart Disease	.. 1
Miscellaneous group-anaemia beri beri thyrotoxicosis etc.	.. 34
Unknown etiology	.. 45

The weights of the livers and spleens were recorded from 31 autopsies, and were analysed in relation to their clinical palpability.

The histopathology was studied in 61 cases, which included 31 autopsies and 30 needle biopsy specimens. Biopsies were done using the Vim Silverman Needle (Wahi[22], Wahi and Mathur[24]) and fixed in 10 per cent formal saline. The microscopic sections were stained as a routine with hematoxylin and eosin stain, Van Geison stain and Foot's reticulum stain.

RESULTS

Among the 266 consecutive postmortem examinations done at the Sarojini Naidu Hospital, Agra, the diagnosis of cirrhosis of the liver was made in 42 cases i.e. 15.7 per cent of the total. These included portal cirrhosis—20 cases, post-necrotic scarring—16 cases, biliary cirrhosis—4 cases, syphilitic cirrhosis—1 case, and infantile cirrhosis—1 case. There was no case of pigmentary and cardiac cirrhosis. In 31 of these autopsies, heart disease was the cause of death, and in none of these was any evidence of cirrhosis of the liver recorded.

In a critical clinical study of 690 cases of congestive heart failure, the liver was found clinically palpable in 421 (61 per cent), the spleen in 54 (7.4 per cent) and both the liver and spleen together in 48 (6.9 per cent) cases. These figures excluded 14 livers and 11 spleens, which could definitely be attributed to causes like infective hepatitis, malaria, kalazar, amœbic hepatitis etc. (Wahi and Mathur[25]).

TABLE III—*Incidence of liver enlargements in 690 cases of congestive failure.*

Etiology	Number of cases	Palpable livers	Percentage.
Rheumatic	234	161	68.8
Cor Pulmonale	222	150	67.5
Hypertensive & Coronary	142	74	52.1
Syphilitic	6	3	50.0
Sub-Bacterial Endo	6	4	66.6
Congenital	1	0	—
Miscellaneous	34	13	38.2
Unknown	45	16	35.5

The clinical enlargement of the liver was commonest among the rheumatic group of cases but no corelation could be established between the size of the liver and the attacks of decompensation or its duration.

Compared to the 61 per cent incidence of clinically palpable livers, the liver enlargement by weight at autopsy was present only in 19.3 per cent of cases, and this figure could be further reduced to 6.4 per cent, if the criterion for hepatic enlargement is taken as 30 per cent above average weight. The average weight at autopsy was 1136 Gm. against our normal average of 1300 Gm.

Free fluid in the abdomen, sufficient to be detected clinically, was associated with 102 out of 690 cases (14.7 per cent) of congestive heart failure. In combinaiton with both liver and spleen enlargements, ascites was recorded in only 19 of the 48 patients with decompensation, most of whom had an icteric tinge.

Apparent increase in the size of the liver, a palpable spleen, ascites and jaundice were not considered adequate criteria for the clinical diagnosis of cardiac cirrhosis, as they might be the result of decompensation alone and not necessarily cirrhosis. Mathur[17] had studied hippuric acid excretion in congestive heart failure, but could establish no corelation between their values and the histological findings. While functional impairment was invariably found in right ventricular failure and corresponded with the extent and degree of cardiac decompensation, it only appeared to be an index of parenchymal damage rather than of its nature.

Under these circumstances the clinical label of cardiac cirrhosis was given, when in addition to a palpable liver and spleen, ascites and jaundice, two other criteria were fulfilled—hardness (with or without granularity) of the liver and repeatedly ascites, recurrent inspite of digitalisation, mercurial diuretics and paracentesis, and out of proportion to the generalised œdema over legs, feet and the body. Only 5 cases of cardiac cirrhosis were thus recorded out of 690 cases of decompensation i.e. 0.72 per cent of the total cardiac cases. During the same period 131 cases were admitted with clinical diagnoses of other types of hepatic cirrhosis i.e. portal cirrhosis—103 cases; biliary cirrhosis—6 cases; infantile cirrhosis—11 cases; syphilitic cirrhosis—1 case; and malarial cirrhosis—16 cases. The last diagnosis is open to criticism in view of the findings of Wahi[23] that malaria causes post necrotic scarring and not a diffuse hepatic fibrosis. To these cases of cirrhosis may be added some cases diagnosed as endemic ascites for Arora's[1] work in the department of Pathology has conclusively proved that in 20 per cent of the cases of endemic ascites, the liver shows changes of diffuse hepatic fibrosis.

The diagnosis of 3 out of these 5 cases of clinically diagnosed cardiac cirrhosis has been confirmed by liver biopsy. These cases were associated with chronic rheumatic endocarditis in 3 cases, hypertensive heart disease in 1 case and constrictive pericarditis in 1 case.

TABLE IV—*Summary of 5 cases diagnosed as cardiac cirrhosis clinically.*

Case No.	Caste, sex and age	Diagnosis	Duration of decompensation	Clinical description of the liver
1	H.F, 45	Rheumatic mitral stenosis with congestive heart failure.	4 years	Liver 5", moderately hard, finely granular, slightly tender.
2	H.M, 11	Rheumatic mitral stenosis, auricular fibrillation with cardiac failure.	2½ years	Liver 4", hard, sharp lower border, not tender.
3	H.M, 60	Hypertensive congestive heart failure	1 year	Liver 3" moderately hard. tender.
4	H.M, 16	Constrictive pericarditis with cardiac decompensation.	6 months	Liver 3", hard, not tender.
5	H.M, 20	Lutembacher syndrome with congestive failure.	6 years	Liver 4", moderately hard, sharp lower border, not tender.

The chief pathological changes seen in the liver in cases of congestive heart failure are:—

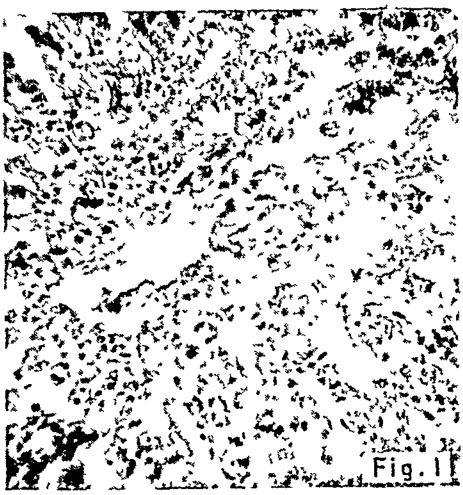
I. Dilatation of the sinusoids with cloudy swelling of the liver cells and hæmorrhages due to rupture of distended capillaries (Fig. 1). These are the earliest changes in passive congestion of the liver, and invariably found in all cases either alone or in conjunction with other microscopic changes described later. The atrophy of liver cells is found adjacent to the central vein of the hepatic lobules, while cloudy swelling is much more marked in the areas close to them. Hæmorrhages found in these cases are due to the overwhelming distension of capillaries with venous blood, their rupture and escape of that blood in the intercapillary spaces formerly occupied by the liver cells.

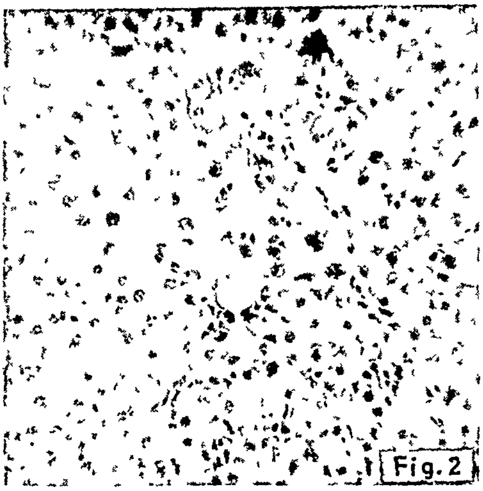
II. The liver cells show extensive cloudy swelling and fatty degeneration with or without much dilatation of sinusoids. The cells are swollen with granular light staining cytoplasm and sinusoids are thinned out (Fig. 2).

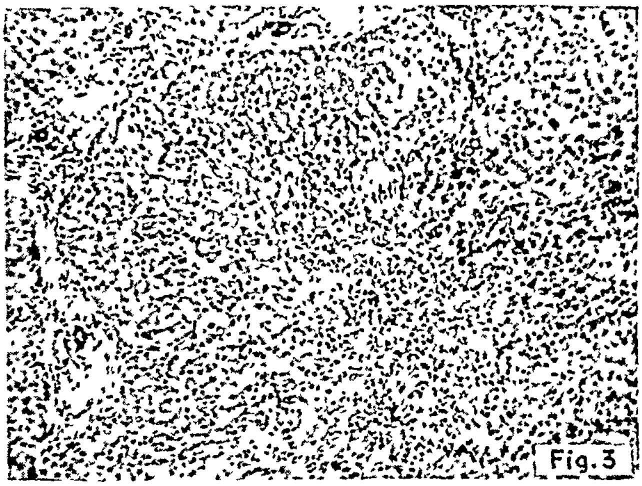
III. Necrosis of the liver cells with or without cellular infiltration. Nuclear changes are evidenced by fragmentation, distortion of shape and disappearance. The cytoplasm is granular, the cell outline distorted, and the polygonal shape lost. This necrosis is most marked in the central third of the hepatic lobules (Fig. 3). Patches of cellular infiltration consisting of monocytes, lymphocytes and plasma cells were present (Fig. 4).

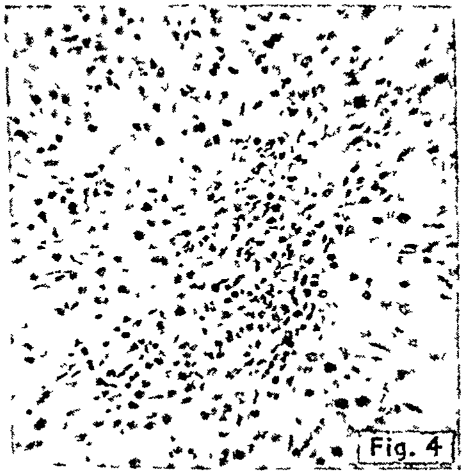
IV. Hepatic fibrosis.

(a) **Central fibrosis.**—Fibrosis when present is most commonly









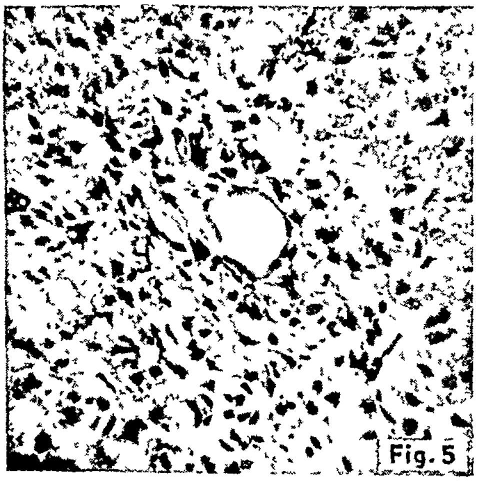


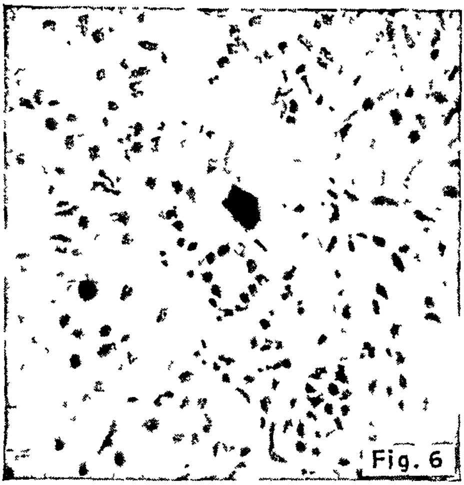
Fig. 1. Dilatation of sinusoids with cloudy swelling of liver cells. Hematoxylin and eosin stain x 50.

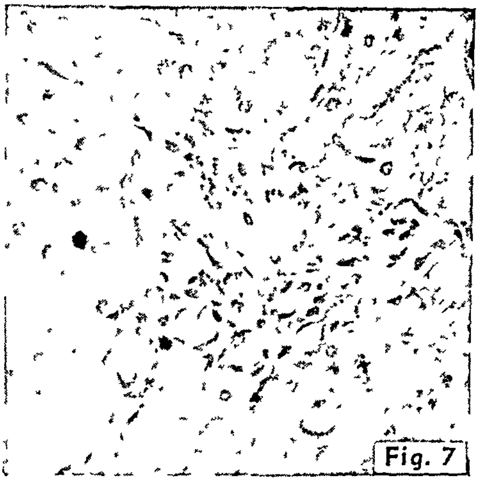
Fig. 2. Liver cells showing extensive cloudy swelling and fatty degeneration. The sinusoids are thinned out. Hematoxylin and eosin stain x 215.

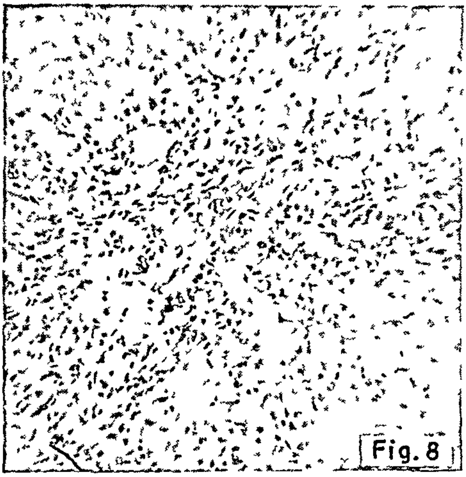
Fig. 3. Liver cells showing central necrosis. Hematoxylin and eosin stain x 100.

Fig. 4. Patch of cellular infiltration consisting of monocytes, lymphocytes and plasma cells. Hematoxylin and eosin stain x 215.

Fig. 5. Replacement fibrosis in the central third of the liver lobule. The dilated central vein can be seen. Hematoxylin and eosin stain x 430.







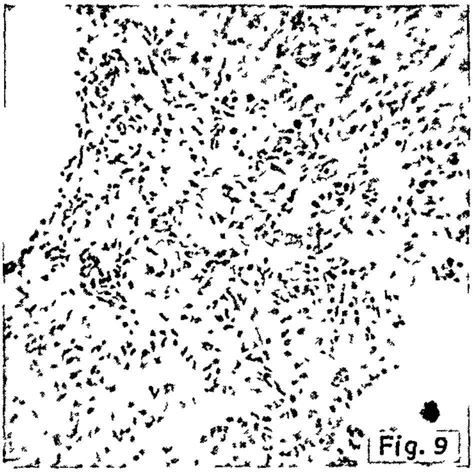


Fig. 6. Periportal fibrosis with extension of the fibrous tissue into the lobule, Van Geisson stain x 430.

Fig. 7. Patch of fibrosis with no relationship to the central vein. Van Geisson stain x 430.

Fig. 8. Perilobular fibrosis. Van Geisson stain x 215.

Fig. 9 Extensive hepatic fibrosis with destruction of the architectural pattern. Hematoxylin and eosin stain x 215

met with in necrotic areas (post-necrotic scarring) and around the central vein. In the early stage there is condensation of the reticulum, while in the late stage adult fibrous tissue is demonstrated by Van-Gieson stain (Fig. 5).

(b) **Periportal fibrosis**—Increase in periportal fibrous tissue of the adult type has been met with in a few cases either alone or usually in combination with post necrotic fibrosis. In the latter case the fibrosis in the central part of the lobule was greater. Occasionally connective tissue bridges have been noted between the central field and portal triads (Fig. 6).

(c) **Patchy fibrosis**—Patches of fibrosis in association with patches of necrosis are not an uncommon finding (Fig. 7).

(d) **Perilobular fibrosis**—It is not a common feature but has been seen in a few of our biopsies. (Fig. 8).

(e) **Extensive hepatic fibrosis** with destruction of architectural pattern. This was met with in three biopsy cases. It was usually associated with post necrotic fibrosis and periportal fibrosis seen in the same specimen under different fields of the microscope (Fig. 9). We did not come across true cirrhosis (diffuse hepatic fibrosis) with regenerating liver lobules.

COMMENTS

Hepatic fibrosis, as a result of repeated attacks of congestive heart failure or prolonged progressive decompensation without apparent remissions, is a definite identity. We are also convinced that the extreme structural distortion and the extensive fibrosis and regeneration uniformly seen in Laennec's cirrhosis does not develop in cardiac decompensation.

Under such circumstances there is no wonder that the criteria for the diagnosis of cardiac cirrhosis and their interpretation have differed with different authors, Lambert and Alison[14] and Menne and Johnston[18] found them non existent; Boland and Willius[3] and White[26] considered them uncommon; Kersner[9], Garvin[7], Kolessky and Barnebee[12], and Kotin and Hall[14] held them moderately frequent.

We would like to suggest that the term cardiac cirrhosis cannot be properly applied to the liver, which is the seat of chronic passive hyperemia, as there is no fixed pattern of fibrosis. This term should therefore be dropped. However, hepatic fibrosis of cardiac decompensation is not uncommon. It may be classified according to its site as:—(1) Central (2) Periportal (3) Patchy (4) Perilobular (5) Extensive.

The primary injurious factor is the passive hyperemia itself. Strong clinical, anatomical and experimental evidence has been produced by Oertal[19], Bolton[5], Lambert and Allison[14], Keefer and Resnik[11], MacCallum[15] and others in favour of the conception that the changes are probably due to prolonged anoxæmia, which accompanies venous stasis and is most severe in the central regions. The blood is not sufficiently aerated in the lungs due to the slowing of the circulation, oedema of the lungs and shallow breathing. The capillary stagnation produces high oxygen utilisation and thus greater reduction of blood. The blood passes very slowly through the sinusoids, so whatever available oxygen is there, is taken up by peripheral cells and none is made available for the central cells, which thus get necrosed. Degeneration and necrosis of the parenchyma are followed by condensation of the stroma and finally by proliferation of the fibrous connective tissue. Post necrotic fibrosis especially near the central veins is therefore the commonest site for hepatic fibrosis.

Himsworth and Glyn[8] have suggested on the basis of experiments on rats that the restriction of circulation through the liver produces a deficiency state—deficiency of amino-acids particularly methionine, which will govern the distribution of the necrosis of liver cells followed by fibrosis. Malnutrition is further caused by restriction in diet, lack of appetite and impaired absorption in congestive heart failure. That malnutrition plays some part is further supported by our finding in quite a number of these cases of fatty changes, which are a recognised pre-cirrhotic condition in cases of dietary cirrhosis. This is important from the point of view of treatment of these cases.

The impairment of circulation predisposes the liver to infection and injurious agents. It is possible that additional factors in necrosis and ultimate fibrosis are toxins, as suggested by Mallory.[16]

When, as a result of multiple factors associated with repeated episodes of decompensation, there is extensive hepatic fibrosis, the clinical diagnosis is suggested by the presence of a hard liver, a palpable spleen, jaundice, the repeated appearance of ascites out of proportion to the œdema in other parts of the body and inspite of digitalisation, mercurial diuretics and repeated paracentesis.

SUMMARY

Six hundred ninety cases of congestive heart failure have been clinically analysed to determine the existence of cardiac cirrhosis and to formulate the criteria for a such a diagnosis. The following are considered essential requirements—a palpable hard liver with or without granularity, a palpable spleen, ascites, jaundice, and the repeated filling of the abdomen, inspite of digitalisation, mercurial diu-

retics and paracentesis, out of proportion to the generalised oedema over the legs, feet and the body.

Sixty-one specimens of liver obtained at autopsy or biopsy were studied to see the type of changes produced in the liver. Essential histological changes are dilatation of sinusoids with cloudy swelling of liver cells and hæmorrhages. In more advanced cases there is central necrosis. Cases of longer duration show fibrosis, which may be central, periportal, patchy, perilobular or extensive hepatic fibrosis with destruction of architectural pattern. There is thus no fixed pattern of fibrosis.

In view of the above findings, it is suggested that the term cardiac cirrhosis as taken to mean a set pattern of fibrosis resultant on congestive heart failure be dropped. Instead the condition be called as 'hepatic fibrosis of cardiac decompensation.'

REFERENCES

1. Arora, M.M.: Thesis for M.D., Agra University, 1949.
2. Bacqueral (1840)—quoted by Fishberg, 1940.
3. Boland, E.E., and Willius, F.A.: Changes in the liver produced by chronic passive congestion, Arch. Int. Med. 62: 723-739, 1938.
4. Boles, R.S., and Clark, J.A.: Role of alcohol in cirrhosis of the liver. J.A.M.A. 107: 1200-1203, 1936.
5. Bolton, C.: J. Path. & Bact. 19: 258, 1914.
6. Fishberg, A.M.: Heart Failure, 2nd Edition, Henry Kimpton, London, 1940.
7. Garvin, C.F.: Cardiac Cirrhosis, Am. J. Med. Sc., 205: 515-518, 1943.
3. Himsworth, H.P., and Glyn, L.E.: Toxipathic and Trophipathic Hepatitis, Lancet 1: 457-461, 1944.
9. Karsner, H.T.: Human Pathology, 6th Edition, J.B. Lippincott Co., Philadelphia, 1942.
10. Katzid, H.M., Waller, J.V., and Blumgart, H.L.; "Cardiac Cirrhosis" of the Liver, Arch. Int. Med. 64: 457-470, 1939.
11. Keefer C.S., and Resnik, W.H.: Jaundice following pulmonary Infraction in patients with myocardial insufficiency, J. Clin. Invest. 2: 389-407, 1926.
12. Kolestsky, S., and Barnebee, J.H.: "Cardiac" or Congestive cirrhosis, pathologic and clinical aspects, Am. J. Med. Sci., 207: 421-430, 1944.
13. Kotin, P., and Hall, E.M.: Clinicopathologic study of cardiac cirrhosis, Am. J. Path. 26: 718-719, 1950.
14. Lambert, R.A., and Allison, B.R.: quoted by Kolestsky and Barnebee (1944).
15. MacCallum, W.G.: A Text Book of Pathology, 7th Edition, W.B. Saunders Co., Philadelphia, 1940.
16. Mallory, F.B.: Bull. John Hopkins Hosp. 22: 69, 1911.
17. Mathur, K.S.: Hippuric acid synthesis test as an aid to prognosis in congestive heart failure, Ind. Med. Gaz. 83: 262-266, 1948.
18. Menne, F.R., and Johnston, T.W.: Cirrhosis of liver, its character of incidence in 6000 autopsies, North West Med. 32: 129-137, 1933.

19. Oertel, H.: Arch. Int. Med. 6: 293, 1910.
20. Ophuls, W.: A Statistical Survey of Three Thousand Autopsies, Stamford University Press, 1926.
21. Pick, F.: (1896)—quoted by White, 1945.
22. Wahi, P. N: Needle Biopsy of liver, technique and diagnostic application, Ind: Med. Gaz. 81: 130-134, 1946.
23. Wahi, P.N. Unpublished communication, 1950.
24. Wahi, P.N., and Mathur, K.S.: Histopathological Changes in liver in congestive heart failure, Ind. Med. Gaz. 82: 715-718, 1947.
25. Wahi, P.N., and Mathur, K.S. Ind. Heart J 1: 230, 1949.
26. White, P.D.: Heart Diseases, 3rd Edition, MacMillian Company, New York, 1945.

OMISSIONS

STUDIES IN B-COMPLEX METABOLISM by R. G. Chitre and B. Y. Nadkarni, Ind. J.Med. Sc. Vol. 5, 67-76, March 1951.

ACNOWLEDGMENT

The authors feel great pleasure in thanking Dr. R. G. Dhaigude, Dean, K.E.M. Hospital and Seth G.S.M. College, for the facilities and encouragements in the present inquiry.

The authors are grateful to Dr. E. P. Bharucha, Asst. Hon. Physician, K.E.M. Hospital, for a substantial grant that made this inquiry possible.

Thanks are also due to Dr. T. J. Thompson Wells of Volkart Bros. for liberal supply of vitamins gratis, required for the purpose of the inquiry.

ACUTE TRAUMATIC BRAIN ABSCESS

REPORT OF A CASE

K. N. Udupa and Jai Lal[*]

In World War I, there was little uniformity of opinion regarding the management of abscesses following penetrating wounds of the brain. At that time it was believed that operative recovery after traumatic brain abscess was extremely rare and Sargent and Holmes[4] reported a mortality of 97.5 per cent, following drainage of pus in such cases. However, the experience in World War II, where the sulphonamides and penicillin played a great role, has completely changed the whole outlook and the mortality has fallen down to 25 per. cent. Under the cover of chemotherapeutic drugs, it is now possible to treat these patients successfully by aspiration, drainage or even excision of the site of the lesion at comparatively early stages.

CAUSATION

Amongst the causative factors of traumatic brain abscesses, high velocity penetrating and gun-shot wounds of the brain are the commonest. This is especially so where debridement was incomplete or performed late. Abscesses in such cases occur early, from the tenth day to the twenty-fifth day of injury and are usually associated with wound infection. Such abscesses usually do not occur after closed injuries of the skull.

Infection reaches the brain directly by implantation through the wounds of the skull, meninges and brain. Once the brain tissue is infected there is no difference from inflammatory manifestations elsewhere. Starting with an inflammatory leucocytic infiltration, softening of the brain substance follows and ultimately results in a cavity containing pus. In the acute stage there is no distinct wall, and the adjacent brain tissue and the meninges become markedly oedematous. In favourable cases the abscess tends to become localised while in the more serious ones the abscess spreads rapidly till it bursts either into the ventricular cavities or the sub-arachnoid space. This is a serious complication and is usually followed by death. Any part of the brain may be affected depending upon the original site of injury; the parietal and the frontal lobes, however, are the commonest sites of injuries and in these regions abscesses developed in 33 cases as reported by Webster and Gurdjian.[5]

---

[*] **Civil Hospital, Mandi, Himachal Pradesh.**

SYMPTOMS

Symptoms of this disease fall into three groups; those due to infection, those due to increased intracranial pressure and those due to focal irritation. All these are usually present in some degree, but any one may predominate depending upon the stage of the disease. Thus in the early or first stage, the signs and symptoms of systemic infection predominate, and there is diffuse infection in the traumatised area of the brain and its meninges with all the signs and symptoms of a systemic infection. Rise in the temperature, rapid pulse, headache, vomiting, muscle twitching and convulsions are some of the symptoms of this stage. A leucocytosis is almost always present. The second stage is one of localisation and encapsulation. The patient gradually becomes afebrile and may fall into a quiet coma. Signs of increased intra-cranial pressure like headache, vomiting, and a slow pulse predominate. In the third stage the rapidly spreading abscess if untreated ruptures into the meninges, ventricles, or brain substances, in which case the course again becomes febrile and soon runs on to a fatal termination. If properly treated in the second stage recovery is almost complete with very few residual signs except where vital and important centres were involved.

DIAGNOSIS

Awareness of brain abscess as a clinical possibility after trauma to the brain is an important first step in the diagnosis. A careful history and a careful neurological examination are very essential for making a diagnosis. Signs of increased intra-cranial pressure, perversion of special senses, delirium of a quiet nature, unilateral convulsions, incomplete hemiplegia (paresis) and coma are important clinical findings. Lumbar puncture gives additional information, and should be done very carefully, only 1 to 3 cc. of fluid being withdrawn, as it is well known that in all cases with increased intra-cranial pressure there is grave risk of sudden increase of pressure upon the medulla, and in the presence of an abscess there is an additional risk of provoking the spread of meningitis. The fluid pressure will be increased as also the cell count and the quantity of total proteins. However, unlike meningitis, normal cerebro-spinal fluid should not exclude the possibility of an acute brain abscess. A roentgenogram of the skull will be an additional help for localisation. A ventriculogram and electro-encephalogram will also help in localising the abscess. If feasible an exploratory tap should be tried; often it proves a definite diagnostic measure. In the early stages, an abscess is differentiated with difficulty from purulent meningitis, where irritative signs with high temperature and rapid pulse are common. A useful point to remember is that in an established acute brain abscess, pressure symptoms predominate with normal temperature, low pulse and quiet type of coma. This condition should also be differentiated from sinus thrombosis, subdural hæmatoma, and sometimes even from brain tumours.

TREATMENT

The principle of treatment of acute traumatic brain abscess should be that the simplest surgical procedure be used first, followed by more radical procedures if and when required. In the early stages large doses of penicillin and sulphadiazine are necessary till the abscess becomes localised, which may be verified by the various symptoms. At this stage, simple tapping of the abscess with penicillin instillation should be given a fair chance. If the symptoms still persist or become increased, simple drainage through the original site of the wound should be attempted. An opening ½" — 1" in diameter should be made in the skull, through which a canula or blunt needle is passed into the brain through the adherent meninges in search of the abscess, and as soon as pus comes out the opening is slightly enlarged, and a soft rubber drain introduced into the abscess cavity. All these measures should be done very carefully lest traumatisation of the abscess wall should occur. The wound is dressed every day, the drainage tube being gradually shortened and finally removed as recovery takes place.

If drainage does not improve the condition, perabrodil may be injected into the cavity and a roentgenogram taken to measure the size of the abscess cavity. After this, excision of the whole abscess wall avoiding injury to the vital centres may be undertaken under cover of penicillin locally and systemically.

This latter procedure, however, is required only rarely if the drainage is undertaken properly and in time. The general management of the patient also plays a great role in achieving success. As already stated adequate systemic doses of penicillin and sulphadiazine, maintenance of proper nutrition, fluid and electrolytic balance are some of the most important factors. Unconscious patients must be nasally fed and the prevention of complications such as bed-sores, various pulmonary manifestations, mouth infection etc., call for careful nursing.

CASE REPORT

A patient named K. R., male, aged 43 years, was brought in walking and fully conscious by the police for multiple head injuries inflicted four days previously by a very strong cutting instrument called a "Gandasa." At that time he bled profusely and the next morning a "Vaid" was called in who stitched the wounds as such.

Examination revealed:—

(1) An incised wound 4½ x ½" x 1¼ deep, on the forehead extending vertically downwards and to the right upper eye-lid for about ½". The frontal bone underneath was also cut for a length of 3".

(2) An oblique wound 4" x ½" x 1¼" on the forehead extending obliquely downwards and to the left, cutting the outer half of the left upper eye-lid. Again the frontal bone was cut for a distance of 3".

(3) Two more incised wounds on the back of the neck of similar size cutting only the muscles at the back of the neck.

TRAUMATIC BRAIN ABSCESS
Showing the site and extent of injuries on the forehead.

As all the above wounds contained free pus, the stitches were removed to encourage drainage, when the dura could be seen covered with pus and pulsating underneath the injured frontal bone. Thus there was a direct communication between the outside and the interior of the cranium. The pulse rate was 94 per minute, the temperature was 100.6°F. Both the pupils were equal and reacted to light and accommodation. The patient was conscious with no paralysis or loss of sensation. Reflexes were normal and no abnormality was found in his temperament or behaviour.

At this stage the wound was dressed with an aequeous solution of acriflavine and penicillin 50,000 units was administered 3 hourly, intramuscularly.

The patient's condition was much the same till the evening of the 7th day after injury (4th day of his admission). Temperature ranged from 98.4°Fto101°F., and his pulse rate remained between 96 and 120 per minute inspite of the injection of penicillin, 50,000 units, 3 hourly. On the morning of the 8th day a change in his mental condition was noticed, when he became drowsy and answered questions with some difficulty and passed urine and stool unconsciously in bed. The left pupil was slightly dilated, but reacted to light. Reflexes in arms and legs were present, but the superficial abdominal and cremasteric reflexes were absent on the left side and present on the right side. No evidence of loss of sensation or motor power was found. His pulse rate remained between 64 and 84 per minute on that day with temperature ranging from 98oF. to 98.8oF. 25 cc. of 50 per cent glucose was given intravenously and 4 ounces of a saturated solution of magnesium sulphate was given per rectum. Penicillin was continued as before.

On the 9th day, except for more drowsiness, the patient's condition was much the same but the pulse rate dropped to 56 and for the next 2 days his condition gradually deteriorated. He became more drowsy and only with loud shouting could he be awakened, when he would utter a word or two and sleep again. He was unable to take food or drink and he continued to pass urine and fæces in bed. Examination on the 11th day showed absence of reflexes on the left arm and leg, where paresis had set in, but thermal and pain sensations (deep pin pricks) were present. The right side was normal. The pulse rate was between 54 and 60 per minute The treatment was as before, with the addition of nasal feeding. Glucose, saline, milk, and fruit juices were given through the Ryle's tube. The mouth was cleaned frequently and the back was attended to properly to prevent bed sores. A lumbar puncture was also done on the 11th day and about 3 cc. of fluid removed. It was found to be clear and under great *tension. The cellular contents were above normal, and were mostly poly*morphonuclear leucocytes. From this day we started sulphadiazine, two tablets four times a day in place of penicillin because of the non-availability of the latter drug.

On the 12th day, the drowsiness deepened, and he could not talk although it appeared that he wanted to say something. A diagnostic aspiration with a No. 1 needle through the broken frontal bone into the right frontal lobe showed frank pus after the needle had entered about an inch of brain substance. As much pus as could be aspirated through the needle was removed and 100,000 units of penicillin was introduced locally. The bacteriological examination of the pus showed almost all the common pyogenic organisms like, streptococci, staphylococci, pneumococci, B.coli and other gram negative bacilli. The treatment was continued as before.

On the morning of the 13th day, the patient was deeply unconscious and all the previous symptoms were aggravated. His eyes were shut all the time. An aspiration of pus was again attempted as before and about 7 cc. of white pus was drawn out. With this the patient was able to open his eyes. At this stage it was thought that only aspiration would not be sufficient to save the life of the patient and that open drainage was necessary. Hence the patient was immediately transferred to the operation theatre where the head was shaved and cleaned. With local novocaine infiltration, a flap of skin with a pedicle was reflected downwards from the site of the injury on the forehead. The frontal bone underneath was found broken in two places. The cranial cavity was entered through in the region of the right frontal sinus after snipping both the broken outer and inner plates for an area of about ¾" in diameter. Aspiration was again attempted by introducing a needle for a distance of about 1" backward and upward and pus came out freely. Therefore an incision was made along the needle with a bistoury for a depth of 1 inch.

About 20 cc. of very foul smelling yellowish green pus was immediately evacuated. A rubber glove drain with gauze in it was introduced into the abscess cavity after instilling 100,000 units of penicillin. The wound was then dressed as usual.

On the 2nd day after open drainage, there was considerable improvement in the general condition of the patient, when he could drink milk and water by himself and speak freely. However the paresis continued as also the passage of urine and stools in bed. Intramuscular injections of penicillin, 50,000 units every 3 hours were again resumed when this drug became freely available. The drainage tube was removed with the dressing.

Three days after operation, the patient gradually improved. He was able to recognise persons around him and on the 4th day he stopped passing fæces and urine in bed. On the 5th day he started to regain power of the left arm and left leg. Reflexes gradually returned in both the arms and legs. 15 days after the drainage he was quite normal except that there was still weakness of the left side of the body. At this stage the wound on the forehead completely healed. He was encouraged to use the left arm and leg as much as possible. Two months later he was again seen in the Out-Patients' Department with complete power of the left arm and left leg and was leading a normal life.

COMMENTS

This is a typical case history of traumatic brain abscess following an improperly treated penetrating wound of the brain. Intracranial symptoms developed on the 7th day of the injury, and reached a climax on the 13th day. The abscess was located in the right frontal lobe, and the first sign announcing intra-cranial pus formation was slow pulse and drowsiness. As a result of oedema and vascular engorgement in the precentral gyrus (motor area) of the right side by the spread of infection from the right frontal lobe, the patient developed paresis on the left side of the body. Treatment consisted of aspiration of the pus which did not give much relief. Therefore open drainage and penicillin instillation locally was resorted to with gradual but complete recovery. Throughout the illness systemic penicillin and|or sulphadiazine were given. Along with this every care was taken to maintain a proper nutritional, electrolytic and fluid balance and to prevent any further complications.

SUMMARY

(1) Patients with acute traumatic brain abscess have a better chance of survival now than two decades ago. This is partly due to the discovery of chemotherapeutic drugs and partly due to a better understanding of the management of these patients.

(2) Awareness of this condition as a clinical possibility following trauma to the brain is a prerequisite in diagnosing this condition.

(3) In the treatment, the simplest measures, like aspiration should be given a fair chance. If not successful open drainage should be resorted to and if still no improvement

occurs local excision under cover of penicillin should be tried as a last resort.

(4) A typical case history of acute traumatic brain abscess is described and a detailed description of its management recorded.

REFERENCES

1. Aird, I.: A Companion in Surgical Studies, 1st Edition, Edinburgh, E & S Livingstone Ltd., 1949.

2. Cairns, H.: quoted by Webster *et al*

3. Christopher, F.: A Test Book of Surgery, 4th Edition, Philadelphia and London, W. B. Saunders & Co., 1945.

4. Sargent, P., and Holmes, G.: quoted by Webster *et al*

5. Webster, J. E., and Gurdjian, E. S.: The Surgical Management of Intracranial Suppuration. A Collective Review, Int. Abst. Surg., Surg. Gynec. Obstet. 90: 209-235, 1950.

MYCOTIC INFECTIONS

H. S. Andleigh*

The various fungous infections form such a large group of diseases that they naturally deserve some importance being attached to them. This is, however, not the case here in India. From the clinical point of view the common fungous infections may be classified under three headings:—

1. The superficial mycoses
2. The intermediate mycoses and
3. The deep mycoses.

Among the superficial mycoses may be mentioned the following infections:

1. Tinea capitis
2. Tinea barbae
3. Tinea glabrosa
4. Tinea cruris
5. Tinea lambricate
6. Tinea favosa
7. Tinea versicolor
8. Erythrasma
9. Trichomycosis axillaris.
10. Piedra.

The intermediate mycoses include diseases, which for the most part are not strictly superficial and certain other diseases which although they are more invasive and deep-seated than the superficial mycoses are still not truly systemic. The moniliases are placed in this group because they include both superficial and systemic diseases. Included in this group are the following mycoses:

1. Moniliases,
2. Chromoblastomycoses, and
3. Maduramycoses.

The deep-seated mycoses include the truly systemic fungous infections. Each disease is a clinical entity and with the exception of true actinomycosis, each of the deep-seated mycoses is caused by a specific organism. This group includes the following infections:—

1. Actinomycosis
2. Sporotrichosis
3. Blastomycosis
4. Histoplasmosis
5. Coccidioidomycosis
6. Granuloma paracoccidioides.
7. Torulosis.
8. Rhinosporidiosis.
9. Aspergillosis.

It will thus be seen that a group of diseases consisting of so many clinical entities should be given its due importance.

The superficial mycoses are of common occurrence and one can see a number of tinea infections in the outpatients' department of any hospital. They are of great importance not only because of their high incidence but also because they simulate, clinically, other skin infections, so much, that it is essential to confirm their clinical diagnosis by laboratory examinations. Moreover, they are important from the epidemiological point of view and as such it is not only necessary that they should be correctly diagnosed, but that the diagnosis be made as quickly as possible.

---

*Department of Pathology, Sawai Man Singh Medical College, Jaipur.

The problem with the deep mycoses is a little different, in as much as their incidence is not as high as that of the superficial mycoses. During a lifetime of work in private and hospital practice, a physician may see only a few patients with one of the deep fungous infections. Besides this, numerous mycotic infections of the lung resemble pulmonary tuberculosis so closely both clinically and radiologically, that it is impossibe to differentiate between the two conditions except with the help of laboratory examination. Among the laboratory methods, the histological examination of the biopsy material alone may not prove very helpful. Weed. Baggenstos, and Bangher (1949)[4] refer to a post-mortem study of 35 cases in which a clinical diagnosis of actinomycosis had been entered. Their investigation was limited to histological examinations and staining reactions. In 21 of the cases actinomycosis was demonstrated with a fair degree of certainty and in 3 the organism was identified with considerable doubt and in the remaining 11, it was not found. The authors have stressed the importance of a bacteriological diagnosis based on culture. Again Weed and Dahlin (1950)[5] record 15 instances in which the pathological diagnosis, when based merely on the histological examination of material, obtained at biopsy was incorrect, and the true diagnosis was made only after identification of the causative organism in culture or in the inoculated guinea pig.

Two interesting cases are being presented below with a view to illustrate the necessity of laboratory examination.

Case 1. K, aged 40 years, a Hindu, female, resident of P. S. Etawah, District Kotah, Rajasthan, was admitted on the 16th of July, 1950 to the surgical wards of the S. M. S. Medical College Hospital, Jaipur, complaining of a hard painful swelling on the left palm.

Present Findings: A hard painful swelling was present on the left palm for the last two years. The condition of the patient at the time of examination was fairly good and general and systematic examination of the patient did not reveal anything abnormal either in the cardio-vascular, alimentary or excretory systems. The blood pressure was; systolic 120 mm. of Hg., and diastolic, 84 mm of Hg. Local examination of the lesion showed the presence of a swelling about the size of a small hen's egg, filling the right thenar eminence. The swelling was hard and appeared to be fixed to the deeper structures (bone). Around the margin of the swelling there were small furuncles about 8 to 10 in number. The swelling was slightly tender. There was no ulceration and no sinuses were present.

History of Present Illness: The patient stated that about 2 years back she noticed a few small furuncles appearing on the left thenar eminence. Later on a swelling appeared which was hard and painful. She never noticed any kind of granules coming out from any part of the lesion.

Laboratory Findings:

Haemoglobin percentage (Sahli's)	58
Total W.B.C. Count	5,100 per c.mm.
Differential W. B. C. Count.	
Polymorphonuclears	46%
Lymphocytes	54%
Bleeding time	2.50 minutes
Coagulation time	3.00 minutes

X-Ray Findings: The Roentgenogram of the left hand showed periostitis 3rd metacarpal bone.

Treatment. In view of the local examination and radiologist's report, a provisional diagnosis of osteoma was made and the swelling was excised. At the time of operation a few yellow granules were seen embedded *in the tissues* and these were removed along with the tissue. The excised part was sent for histo-pathological examination and was reported as follows:

Histo-pathological examination of the tissue showed a mass of chronic granulation tissue which showed some small round cell infiltration and some areas of fibrosis. No giant cells could be seen anywhere. In the central area of these chronic granulomatous lesions were found foci of minute abscesses filled mostly with polymorphonuclear cells in all stages of preservation and degeneration. In two of these abscesses cavities were found the typical colonies of actinomyces. These appeared as irregularly lobulated masses of deep purplish staining material when examined under the low power. When examined under the oil immersion lens, these colonies of actinomyces appeared like masses of twisted mycelia. On the peripheral part of this mass was seen an area of radiating thick strands of eosinophilic material which suggested an attempt at club formation.

It is unfortunate that cultural examination of the discharge containing the granules could not be done and one can only say that it was a case of actinomycosis. In the absence of cultural examination it is difficult to say anything about the species of actinomyces which caused the disease in this case.

Case 2. The second case was of a youngster of about 14 years of age, a Hindu male student, who was admitted to the S.M.S. Medical College Hospital, Jaipur, on the 27th of January, 1950 and discharged on the 30th of January 1950. The complaints on admission were:

1. Recurrent growth in the left nostril of 3 years duration.
2. Frequent attacks of epistaxis, and
3. Obstructed breathing especially on lying in bed.

The patient stated that the growth was excised about 5 times previously but reappeared every time. Local examination showed the presence of a fleshy polypus occupying and almost filling the left nostril. The polypus was freely moveable. Since the patient wanted only relief from the

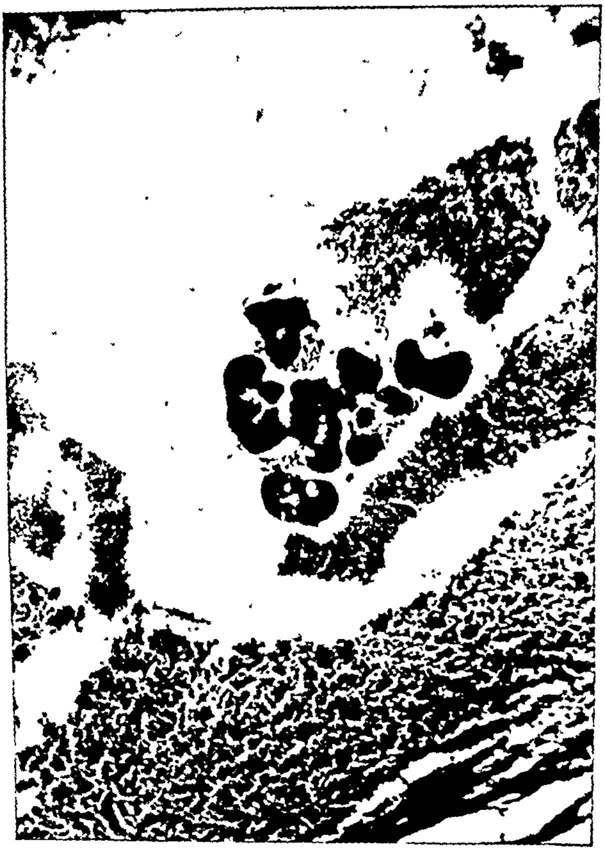
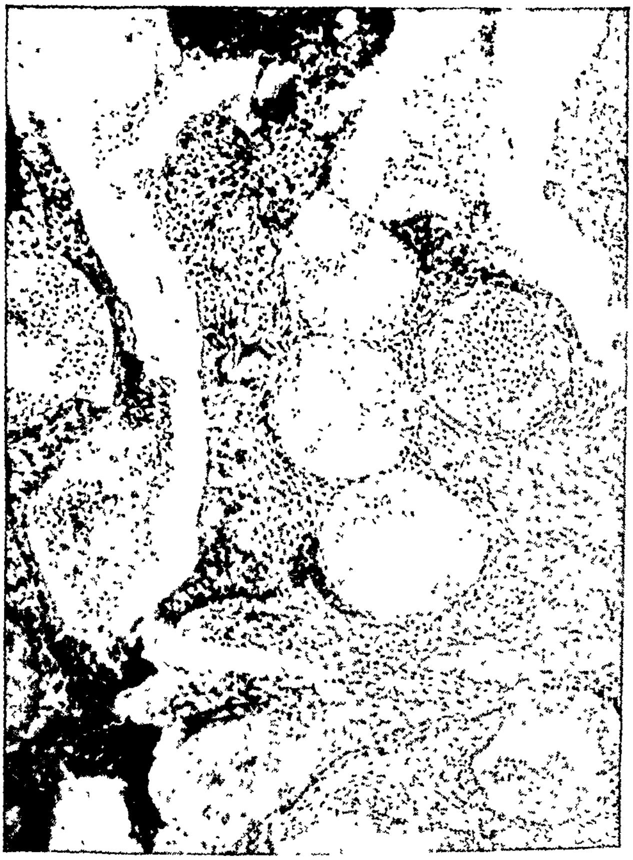


Fig. 1. Mycotic infections.
Microphotograph showing fungous colonies.

Fig. 2. Mycotic infections.
Microphotograph showing sporangia of Rhinosporidium.



obstruction to breathing by the removal of the polypus and was very anxious to leave the hospital without delay, no detailed laboratory examinations could be done. The polypus was excised under general anaesthesia and sent for histo-pathological examination, the report of which runs as follows: "Histo-pathological examination of the tissue showed a matrix of oedematous connective tissue showing mucoid degeneration. Scattered all over the tissue were sporangias with their chitinous walls. The sporangia varied in size from that of a neutrophil to as much as about 120 μ in diameter. Some of the sporangia were empty and were recognised only by their chitinous walls while others were packed with hundreds of spores, each of the size of a red blood cell and had a well developed cell membrane and appeared to be chitinous. The spores appeared to be all of the same size. There was no evidence of any granulation tissue formation and no giant cells could be seen."

COMMENT

Rhinosporidium has not yet been grown in any artificial media.

Fungous infections may be of common occurrence in India, but excepting the infections of the skin and the actinomyces and rhinosporidium infections, the other type of fungous diseases have rarely been reported. It is difficult to account for the apparent absence of cases of deep mycoses in the face and the high incidence of the superfical mycoses. It is possible that cases of deep mycoses may be occurring in India in fair numbers but remain unidentified because of the lack of sufficient and efficient laboratory aids.

The need of at least one central well equipped mycological laboratory in India under the control of a fully trained mycologist can well be appreciated.

REFERENCES

1. Allen, F.R.W.K., and Dave, M.: Treatment of Rhinosporidiosis in man based on the study of sixty cases, Ind. Med. Gaz. 7: 376-395, 1936.
2. Conant, N.F.: Manual of Clinical Mycology, Philadelphia, W.B. Saunders & Co., 1945.
3. Henric, I.T.: Molds, Yeasts & Actinomycetes, New York, John Wiley & Sons, 1947.
4. Weed, L. A., Baggenstos, A. H., and Bangher: Proc. Staff Meet., Mayo Clinic 24: 463-471, 1949.
5. Weed, L. A., and Dahlin, D. C.: Bacteriologic Examination of tissue removed for Biopsy, Am. J. Cl. Path. 26: 116-132, 1950.

PHYSIOLOGICAL MECHANISMS IN PSYCHOSOMATIC PHENOMENA

W. W. Heseltine *

During recent years, great advances have been made in psychiatry and the literature contains a wealth of clinical information which has contributed much towards the study of the mind-body relationship. Clinical evidence alone, however, cannot form a truly scientific basis for psychosomatic medicine and, for this reason, physiological investigations have been undertaken by a number of workers, in an attempt to establish definite connections between the mental and physical functions.

Although this task is, as yet, far from complete, valuable data have been obtained and it is the purpose of this communication to review the information available and to propose certain theories which may assist in elucidating some of the physiological mechanisms involved in psychosomatic phenomena. Since this approach to the problem is a physiological one, it is necessary to consider briefly the functions of the organs apparently involved and to trace connections which may enable these individual organs to operate as a system.

THE BRAIN

By examining brain lesions, by tracing the course of nerve fibres and by animal experimentations, it has been possible to ascertain the functional activity of many portions of the cerebrum, but it would appear that the so-called "silent areas" have a more complex function than the motor and sensory centres. Flechsig postulated that the "association areas" are concerned with higher mental activities, his views being based mainly upon the time of myelination in the embryo brain. Studies of cerebral embryology in relation to function have shown, that, while the afferent tracts are myelinated at birth, the efferent tracts are not myelinated until later. Myelination seems to increase with intellectual progress and is apparently necessary for proper functional activity. The association areas are the last portions of the brain to be myelinated and this may explain the retarded development of concept-association in the child. The fibres which connect the association areas with certain sensory centres may provide a direct pathway for the transmission of sensory impulses to these areas where complex thoughts may be compounded and stored. From the silent areas, moreover, fibres pass to the grey nuclei, which are probably associated with emotional function.

---

* Technical Department, Harker Stagg Ltd., London.

The thalamus and the basal ganglia, of which the most important are probably the lenticular and caudate nuclei, (together forming the corpus striatum) are generally believed to serve important functions in the "emotive system", the existence of which has been suggested by Wallon.[45] It would appear that the corpus striatum is concerned with some of the primitive movements. The hypothalamus also plays an important role in the elemental reactions and there is much evidence to suggest that it has a controlling influence on the activity of the pituitary. Stimulation of the hypothalamic areas produces a condition of rage in experimental animals, while cutting of the fibres connecting the frontal lobe with the hypothalamus of mentally depressed patients may often result in marked elevation of mood. Bard and Mountcastle[5] found that the removal of the telencephalon, excluding the corpora striata, the "rhinencephalon" and the gyrus cinguli from cats produced a state of placidity without the exhibition of pleasure or rage. Extirpation of the gyrus cinguli produced no effect and ablation of various portions of the frontal lobes did not alter the rage-threshold, but bilateral removal of the hippocampus caused an increase in pleasure reactions. Ward[46] observed that stimulation of the rostral part of the gyrus cinguli of the monkey causes pupillary dilatation, pilo-erection, facial movements and other effects, while ablation of the region causes the animal to become less fearful and hostile and apparently less affectionate. From studies of various types of animal brains, it would appear that the corpora striata are concerned in the control of instinctive behaviour, while the neopallium probably plays a part in the control of learned behaviour.

It has been suggested[40] that the hypothalamus is concerned with the regulation of co-ordinated functions, the middle and hind regions being linked with sympathetic activity and the anterior portion with protective functions mediated through the parasympathetic system. It is evident that the hypothalamus is important in psychosomatic phenomena, since severe emotional derangement may often cause rapid increases in weight through dysfunction of the centre controlling water metabolism; similar effects are produced by hypothalamic damage. The pituitary is not involved in this type of obesity, although Verney[44] has shown that certain emotions lead to the discharge of impulses from the hypothalamus which stimulate the secretion of pituitary antidiuretic hormone, so causing retention of fluid.

Intimately connected with the hypothalamus and the corpus striatum is the thalamus, which is a collecting centre of impulses of general sensation. It has been shown[11] that stimulation on the anteromedial portion of the thalamus produces a generalized response in the cortex during electro-physiological experimentations. Spiegel and Wycis[43] found that, although the human electrothalamogram shows waves similar to the alpha and beta rhythms, there is a considerable degree of independence of the thalamic and cortical discharges. By means of the electroencephalograph, Murphy and Gelihorn[33] showed that the cortex, thalamus and hypothalamus are interconnected, while Darrow[10] concluded that, in schizophrenia and related conditions, investigations carried out by various workers may indicate a deficiency in thalamic and autonomic regulation of the cortex, so permitting self-excitation to the point of cortical exhaustion. The regulating influence of the autonomic system appears to be established, the sympathetic effect being mainly inhibitory, but there is also evidence to suggest that abnormal frontal activity affects the hypothalamus in such a manner as to inhibit the sympathetic function and to augment the parasympathetic function.

Lesions of the frontal lobe cause reduction of mental acuity, of powers of concentration and of qualities of leadership, sometimes with loss of memory. Prefrontal leukotomy in schizophrenic patients produces a dull, apathetic individual devoid of all emotion, but symptomatic improvement is often only temporary. McLardy and Davies[30] suggest that either the isolated cortex can later function again by way, of relays of subcortical or intracortical pathways or the pre-operative symptoms can develop again without the participation of the prefrontal regions. The former explanation is the more likely, especially since the symptoms which later develop are nearly always of the same type as those originally present.

Meyer and Beck[32] consider that the orbital region of the prefrontal cortex, the cingular cortex, the thalamus, hypothalamus and the hippocampal area are all important in relation to emotion and personality, and there is much to support this concept. It is undesirable, however, that these regions should be regarded as the only centres of emotional functioning. Nielson and Sedgwick[36] recently studied the instinctual and emotional functioning of an anencephalic monster which survived for 85 days, and they observed that the baby exhibited fear, contentment and discomfort although even thalami were absent. These observations suggested that crude instincts and emotions are patterned in the spinal cord but, as the authors state, this may not be true of adults, since many cerebral nerve elements in the infant are unmyelinated and so functionally immature.

While it may not be possible to localise specifically the seat of emotional activity, there is much evidence to indicate the existence of an "emotive system" with important executive organs in the involuntary muscles, the muscles of expression and the glands of internal and external secretion. The emotions themselves appear to be allied to the conditioned reflexes, of which a detailed study has been made by Pavlov[37],[38] stimuli reaching the "emotive system" by way of the sensory apparatus. This theory is supported by observations made on infants by Rubinow and Frankl[41], Piaget[39] and other workers who have shown that the sensory functions are practicaly non-operative for the first four months of life and that their full development takes about two years. The "emotive system" is, however, functional in the first four months[47] and so the infant is particularly vulnerable to violent environmental stimuli, since the sensory screening apparatus is absent or deficient.

THE AUTONOMIC NERVOUS SYSTEM

The role of the autonomic nervous system in psychosomatic phenomena has led to the concept that sympathetic-parasympathetic imbalance may be a primary cause of emotional disturbances, but it is preferable to consider autonomic activity as part of a reaction pattern with which the whole central nervous system and the endocrine glands are closely associated. The autonomic network is directly connected with the thalamus and other centres which are believed to be involved in emotional phenomena, and the effects of emotion upon gastric function, circulation and other bodily activities demonstrate a physiological mechanism which links the mental and somatic functions and dysfunctions.

Faulkner[14] observed that fear, anxiety and anger frequently cause spasm of the œsophagus and other workers[40] have reported changes in gastric function due to emotional disturbances, but it would seem that the effects upon the digestive mechanism depend upon the nature of the mental stress. Conversely, Ferraro[15] states that stress on the sympathetic nervous system, following the consumption of a full meal, produces anxiety which becomes a conditioned response, while Nathan and Ransford[35] conclude that a certain type of convulsion may be initiated by visceral tensions and irritations. Concepts regarding the existence of a viscero-thalamo-cortical syndrome appear to be supported by the beneficial results[6] obtained in pure anxiety states by means of tetra-ethyl ammonium chloride, which acts upon the autonomic ganglia, and it is interesting to note that bilateral stellate ganglion block with procaine may be of value in mental depression.[25]

Gynæcological dysfunctions are discussed later from the endocrinological view-point, but neurological aspects may be briefly considered at the present juncture. Kroger and Freed[27] have outlined the physiological involvement of functional amenorrhœa on the basis that the hypothalamus may govern emotional response to external environment, the response being expressed through the hypothalamic, sympathetic and parasympathetic systems. These workers suggest that a more direct neurogenic control of menstruation may also exist, this control being partially independent of hormonal changes, and they quote Fuerstner's[1c] belief that emotional factors may interfere with the hypothalamic, rhythmic impulses, so enabling the autonomic system to affect the endometrium directly. Apart from this direct mechanism, the anterior pituitary is probably controlled by the hypothalamus which may thus be regarded as the "master organ" in the female neuro-endocrine system and the seat of neurogenic and endocrine disturbances in many gynæcological dysfunctions of emotional origin. Emotional disturbances may, therefore, produce effects directly upon the sympathetic-parasympathetic systems, causing tubal spasm, changes in endometrial vascularization, muscular contraction of the uterus and other conditions calculated to induce gynæcological disorders; the autonomic imbalance may also produce secondary endocrine imbalance or, alternatively, the stimuli may be communicated directly from the hypothalamus to the pituitary without any apparent primary autonomic involvement, although the latter may arise from the endocrine disturbances.

There can be little doubt that autonomic imbalance is responsible for a variety of other disorders, notably those of the cardiac and circulatory systems with clinical manifestations such as palpitation, tachycardia or bradycardia and vasomotor disturbances. In all cases, the role of the autonomic nervous system appears to be dual, in that the emotions may produce autonomic imbalance or, conversely, the latter imbalance may cause emotional disturbance, and it is thus apparent that the psychosomatic condition may deteriorate through the production of a vicious circle centred round the "emotive system."

THE ENDOCRINE SYSTEM

Nervous stimuli play an important part in the direct or indirect regulation of endocrine activity, but it may be more correct to consider that there is an interplay of reversible effects between the nervous and endocrine systems; for example, the manifestations of hyperthyroidism resemble those of sympathetic stimulation, Simmond's Disease may be almost indistinguishable clinically from anorexia nervosa, emotional stress may induce diabetes mellitus or gynæcological disorders, while the climacteric is frequently characterised by multiple autonomic disturbances.

The precise relationship between the endocrine system and the central nervous system has not yet been fully investigated, but there can be little doubt that the interconnection is a very intimate one. It is known that hypothalamic lesions in guinea-pigs may cause ovarian changes, probably mediated through the pituitary gonadotropins and Hilliarp[21] has conducted experiments in the rat which suggest that the section of luteinising hormone is controlled by a centre in the anterior hypothalamus. Everett et al[12] have shown that in four-day cyclic rats, the ovulating discharge of hypophysial hormones is controlled by neurogenic stimulation and that the stimulus for luteinising hormone may be blocked by means of dibenamine or atropine, while pentobarbital sodium, given on the day of prœstrus, will delay the release of this hormone. In reviewing the evidence to indicate the localisation of a controlling centre regulating the discharge of luteinising hormone, Everett and Sawyer[13] incline to the view that the centre which controls the discharge of an "ovulation stimulus" to the hypophysis is located in the rostral hypothalamus: according to this view, the pathway to the pituitary is represented by the tuber cinereum, median eminence and hypophysial portal circulation. Like the autonomic nervous system, the endocrine system appears to have reciprocal communications with the higher centres and Kent and Liberman[26] have found that œstrus behaviour may be induced in spayed, œstrogen-primed hamsters by progesterone given into the lateral brain ventricle in a dose which has no effect when given subcutaneously. In an investigation into the cause of amenorrhœa, Massenbach and Heinsen[28] studied the carbohydrate and water metabolism of 100 cases and they concluded that amenorrhœa, like other forms of vegetative dysfunction, is caused by disturbances in the diencephalic-hypophysial system. Meyer[32] described the case of a girl with precocious puberty and imbecility at the age of 3 years and reported on the autopsy which was carried out after death at the age of 13 years. The tumour found in the floor of the third ventricle and the other changes observed support the view that a sexual centre is located in the mediobasal tuber cinereum and demonstrates the close linkage between the diencephalon and the endocrine system.

Ashby[4] has suggested that the beneficial effects of electro-convulsive therapy may be due to increased adrenal cortical secretion, the pituitary being stimulated via the hypothalamus to produce corticotrophic hormone, since in 14 psychotic patients subjected to electro-convulsive therapy, there was usually an increased production of both "sugar-active" and "reducing" cortins. It has also been observed by other workers[3] that electric shock therapy causes a rise in urinary uric acid excretion and in creatinine excretion, the circumstances suggesting an elevated production of 11-oxysteroids. Abely[1] ionsiders that certain psychoses of pregnancy are freqnently due to hyperfunction of the acidophile zone of the hypophysis with excessive consumption of adrenal cortical hormones and it has also been suggested[15] that the profound metabolic changes caused by hypofunction of the adrenal cortex affect the brain and other bodily tissues.

Williams and Wright[48] comment on the fact that the types of psychoses amenable to shock therapy are those which are associated with endocrine disturbances and that the adrenals show structural changes in shock and are involved in some psychotic states. Since the type of psychosis most benefited by shock treatment is the type in which the endocrine-autonomic system is involved and since shock apparently acts essentially through that system, these authors consider that there is a close association between the psychosis, the endocrine-autonomic system and the shock therapy. It has not yet been shown, however, that the endocrine reaction to shock is directly responsible for the favourable results, although there can be little doubt that the endocrine response is a vital link, if not the end-point. In Addison's Disease, there are often periods of severe psychic disturbance, such as melancholia or delirium with maniacal excitement and occasionally epileptiform convulsions may occur. Jaira[24] found that only 40 per cent of a series of 50 psychotic patients showed an eosinophil response to adrenocorticotrophin, although the count fell in all normal controls, and it was suggested that this shows an association between mental disease and deficient adrenal cortical function. It has been noted[10] that a key symptom in catatonic schizophrenia is low blood pressure and that there are marked similarities between hypo-adrenalism and certain mental disorders; it may not, therefore, be surprising that clinical improvement as result of the administration of desoxycorticosterone has been reported by many workers.

Cretinism appears to be a classical example of mental retardation and derangement due to lack of an endocrine secretion, especially since excessive thyroid function produces a condition of great emotional excitement and nervous irritability. In these conditions, the thyroid seems to exert a specific activity, but it must be recalled that the various members of the endocrine system are intimately related, with the result that a disorder of one may cause secondary dysfunctions of other glands. Also of importance in considering the influence of the endocrine secretions upon the higher centres are the effects of severe hypoglycæmia, resulting from excessive endogenous production or artificial administration of insulin, which decreases the metabolic rate and oxygen utilization of the brain[30]. This effect alone is considerable, since the brain normally consumes much more oxygen than the general muscle and nerve tissue, but of even greater significance is the production of damage and physical changes, particularly in the ganglion cells. The clinical results of these effects include convulsions, epileptiform seizures, mental deficiency, coma and personality changes,[31],[10],[2], these psychic conditions may persist for many months and, in some cases, the mental state may never return to normal, even though the blood sugar levels are raised again within a comparatively short period. Portis[40] considers it logical to assume that the hypoglycæmia of psychoneurotic patients is due to long-continued vagal stimulation relayed from the hypothalamus, and that there results a psychosomatic syndrome caused directly by the hyperinsulinism, this concept being supported by the fact that atropine produces definite clinical improvement.

It is well-known that emotional trauma may often cause sexual dysfunction and many gynæcological disorders appear to be expressions of psychic disturbances. Psychoses and neuroses, on the other hand may be caused directly or indirectly by endocrine dysfunction; for example, the climacteric may produce a variety of symptoms, including the so-called "involutional melancholia." Disturbances of mental balance may occur at any time when there is pronounced change in sex-steroid production, such as during the puerperium, menstruation, pregnancy and after castration. McCartney[29] found that the gonads in 154 male and 24 female schizophrenic patients showed a high proportion of pathological states and other workers[42] discovered that in about 70 per cent of 129 female schizophrenics, no œstrogen was secreted. It has been shown[46] that testosterone, œstradiol or progesterone reduce the chronaxie of central and peripheral nerves in male or female rats and, furthermore, that correct hormonal balance is necessary for proper function of the nervous system.[7] Steroid estimations in 21 schizophrenic men showed[8] a raised œstrogen level and a lowered androgen output, the hormonal excretion demonstrating a definite approach towards the female pattern. Many accounts have been published regarding the beneficial effects of œstrogens, progestogens and androgens alone or in combination, in the treatment of psychotic disorders; the steroids may simply replace the deficient hormone or they may also exert a controlling influence upon excessive pituitary activity.

The role of the pituitary itself is somewhat obscure. The trophic hormones secreted by the anterior lobe control the activities of the subordinate endocrine glands which, in turn, produce hormones which appear to be intimately concerned with psychosomatic phenomena, and it is known that Simmond's Disease provides a complex picture of psychical as well as physical disturbances. Verney[44] has shown that emotion may lead to the discharge of hypothalamic impulses which stimulate secretion of pituitary antidiuretic hormone, so causing retention of fluid, but the place of the middle and posterior pituitary in the mind-body relationship has not so far been determined. It would appear, moreover, that antagonism may exist between the pituitary and pineal glands and Giardinelli[17], found that pineal extracts controlled or diminished climacteric disturbances regarded as being due to hypophysial hyperactivity; thus, the pineal gland may be important in psychosomatic phenomena.

DISCUSSION

General regulation and adaptation may normally be governed, wholly or partly, by the diencephalic centres, but the lower centres may take over autonomy in certain circumstances and so the physiological mechanism may, by its complexity, defy definition. It would seem logical, however, to consider that in man there exists an "emotive system' comprising certain higher centres, the autonomic network and the endocrine system, and forming a bridge between the complex mental processes and the bodily function. The higher centres, or "emotive area", may then be regarded as receiving impulses from and transmitting impulses to the sensory and other centres and having direct reciprocal communication with the body by way of the autonomic and endocrine systems, these two systems themselves having direct central and peripheral effects one upon the other.

The components of the "emotive system" which offer the most ready means of treatment are the autonomic and endocrine systems and it may later become possible to classify many mental disorders into sympathetic, parasympathetic or endocrine groups, each with clearly defined signs and therapeutic measures. Much evidence is already available toward such a classification but, with few exceptions, particular psychoses cannot yet be associated definitely with clear-cut autonomic|endocrine dysfunctions and so physical and biochemical investigation remains a vital part of psychosomatic therapy.

SUMMARY

A review of the published evidence indicates that there may be a definite physiological mechanism involved in many psychosomatic phenomena. The components most likely to form this mechanism are considered under appropriate headings and the practical implications are discussed.

REFERENCES

1. Abely, P.: Consideration Endocrino-biologiques a propos des Nervoses et des Psychoses de la Puerperalite, Ann. Medico-Psychol., 105: 560, 1947.
2. Allan, F. N. and Crommelin, R.M.: Cerebral Damage from Insulin Shock; Hemiplegia, Aphasia and Epileptic Seizures for 15 months, J.A.M.A. 118: 373-374, 1942.

3. Altschule M.D., Altschule L H. and Tillotson K.J.: Changes in Urinary Uric acid-creatinine Ratio after electrically induced Convulsions in Man, J. Clin. Endocrinol. 3: 487, 1949.

4. Ashby W.R.: The Effects of Convulsive Therapy on the Excretion of Cortins and Ketosteroids, J. Ment. Sc., 95: 275-324, 1949.

5. Bard P. and Mountcastle V.B.: Some Forebrain mechanisms involved in expression of Rage with special reference to suppression of angry Behaviour. Res. Publ. Ass. Res. Nerv. Ment. Dis., 27: 362-404, 1948.

6. Bell E. and Karnosh L.J.: Tetra-ethylammonium Chloride as an adjunct in treatment of psychovisceral manifestations of Anxiety. J. Nerv. Ment. Dis., 108: 367-372, 1948.

7. Chauchard P.: New Investigations of nervous action of Sex Hormones; Ann Endocrinol, 8: 281-282, 1947

8. Chauchard P.: Hormones Sexuelles et Systeme Nerveux: Arch Int. Pharmacodyn., 74: 286-287, 1947.

9. Darrow D.C.: Mental deterioration associated with Convulsions and Hyperglycaemia, Report of 2 Cases; Am. J. Dis. Child., 51: 575-582, 1936.

10. Darrow G. W.: Electroencephalogram and psycho-physiological Regulation in Brain; Am. J. Psychiat., 102: 791-798, 1946.

11. Droogleever J.F.: Electro-encephalography and Epilepsy. A Review of clinical and electro-physiological Data; Folia Psychiat. Neurol. et Neurochir., Neerlandica, Asmterdam, 1949.

12. Everett J.W. and Sawyer S.M.: A neural timing Factor in the Mechanism by which Progesterone advances Ovulation in the cyclic Rat; Endocrinol., 45: 581-595, 1949.

13. Everett J.W., Sawyer C. H. and Markee J.E.: A neurogenic timing factor in control of the oculatory discharge of the luteinising Hormone in the cyclic Rat.; Endocrinol., 44: 234, 1949.

14. Faulkner W.B. Jr.: X-Ray evidence of emotional influence upon esophagial function: Am J. Psychiat, 98: 227-228, 1941.

15. Ferraro A.: Somato-psychic factors in anxiety Neuroses; J. Nerv. Ment. Dis., 107: 228-242, 1948.

16. Fuerstner P.G.: Some neurophysiological aspects of Menstrual Cycle and its disturbances; J. Nerv & Ment. Dis., 99: 588-594, 1944.

17. Giardinelli M.: Clinical Research on the use of Pineal Gland Extracts in the Treatment of climacteric Disturbances; Minerva Med. Turin, 1949.

18. Gorman W.F. and Wortis S.B.: Psychosis in Addison's Disease; Dis. Nerv. Syst., 8: 267-271, 1947.

19. Haynes H.J. and Carlisle C.L.: Treatment of Schizophrenia with Desoxycorticosterone; Med. Bull. Vet. Admin., 18: 141-147, 1941

20. Hess W.R.: Significance of the Hypothalamus in regulation of vegetative Functions, Archiv fuer Klin, Med., 195, 1949.

21. Hillarp N.A.: Studies on the localization of hypothalamic Centres controlling the gonadotrophic Function of the Hypophysis, Acta Endocrinol., 2: 11-23, 1949.

22. Himwich H. E. *et al*: Science, 86: 271, 1937.

23. Hoskins R.G. and Pincus G.: Sex Hormone Relationships in schizophrenic Men, Psychosomatic Med., 11: 102, 109, 1949.

24. Jaria A.: Studies on adrenal cortical function in certain Psychoses, Fol. Endocrinol., 2: 605-613, 1949.

25. Karnosh L.J. and Gardner W.J.: Effects of bilateral Stellate Ganglion Block on mental Depression, Report of 3 Cases; Cleveland Clin. Quart., 14: 133-138, 1947.

26. Kent G. C. and Liberman M.J.: Induction of psychic oestrus in the Hamster with Progesterone administered vio lateral Brain Ventricle; Endocrinol., 45: 29-33, 1949.

27. Kroger W.S. and Freed S.C.: Psychosomatic Factors in functional Amenorrhoea; Am. J. Obst. and Gynec., 59: 328-336, 1950.

28. Massenbach W. and Heinsen H.A.: Amenorrhoea as a Symptom of Diencephalic-hypophysial Dysfunction; Zbl. Gynak., 70: 540-554, 1948.

29. McCartney: Endocrinol., Jan-Feb., 1929.

30. McLardy T. and Davies D.L.: Clinical and pathological Observations on Relapse after successful Leucotomy; J. Neurol, Neurosurg. and Psychiat., 12: 231-238, 1949.

31. Meyer, J.E.: Precocious Puberty with hyperplastic Malformation of the Hypothalamus. A Contribution to the Problem of the sexual Centre and of Neurosecretion in the Diencephalon; Archiv f. Psych. u. Nerv. mit Ztschr. f. Ges. Neurol. u. Psych., 179|3-4, 378-394, 1948.

32. Meyer A. and Beck E.: J. Med. Sc., 91: 411, 1945.

33. Murphy J.P. and Gellhorn E.: Influence of hypothalamic Stimulation on cortically induced Movements and on action Potentials of Cortex; J. Neurophysiol., 8: 341-364 and 431-447, 1945.

34. Murphy F.D. and Purtell J.: Insulin Reaction and cerebral Damage that may occur in Diabetes; Am. J. Digest. Dis., 10: 103-107, 1943.

35. Nathan P.W. and Ransford P.M.: Significance of Convulsions in Infancy; B. M. J., 2: 421, 1949.

36. Nielson J.M. and Sedgwick R.P.: Instincts and Emotions in an anencephalic Monster; J. Nerv. Ment. Dis., 110: 387-394, 1949.

37. Pavlov I.P., Lectures on conditioned Reflexes; Lawrence and Wishart, 1918.

38. Pavlov, I.P.: Conditioned Reflexes; Oxford Univ. Press, 1927.

39. Piaget, La Construction du Reel, Paris, 1936.

40. Portis S.A.: Life Situations, Emotions and Hyperinsulinism, J.A.M.A., 142: 1281-1286, 1950. 4

41. Rubinow O. and Frankl L.: Die erste Dingauffassung beim Saugling, Ztschr. f. Psychol. u. Physiol. der Sinnesorgane, 33: 1-71, 1934.

42. Sears H.A. *et al.*; Blood Estrin Level in Schizophrenia, Am. J. Psychiat, 93: 1293-1303, 1937.

43. Spiegel E.A. and Wycis H.T.: Electrogram of the human Thalamus and Hypothalamus, Am. J. Med. Sc., 219: 108-109, 1'50.

44. Verney E.B.: Absorption and Excretion of Water, the anti-diuretic Hormone, Lancet, 2: 739-745 and 781-783, 1946.

45. Wallon: L'Enfant Turbulent, Paris, 1925.

46. Ward A.A.Jr.: Anterior cingulate Gyrus and Personality, Res. Publ. Ass. Res. Nerv. Ment. Dis., 27: 421-431, 1948.

47. Wildenberg-Kantrow, Iowa Univ. Chil. Welf. Res. Station, 1937.

48. Williams E.H. and Wright C.A.: Endocrine Patterns in some Psychoses, Med. Record, 8: 302-304, 1941.

49. Wolf S. and Wolff H.: Human Gastric Function; Oxford Univ. Press, 1943.

LEVEL OF TERMINATION OF THE SPINAL CORD

N. Das * and Balbir Singh *

Before the year 1894, very little attention was paid to the wide variation in the level of the termination of the spinal cord. Investigators like Nuhn (1849), Pfitzner (1884), and Reid[4] (1889), studied the spinal segments in a few cases to demonstrate the extent of recession of spinal cord during body growth and to determine the position of cord segments in relation to surface land marks. Very little notice, however, was taken of the variation of the level of termination of the cord.

Our present day knowledge of the termination of the spinal cord is based on the work carried out by Thompson[6] and his associates (1894): McCotter[2] (1916); Needless[3] (1935) and Reimann and Anson[5] (1944). The site of termination according to these workers varies from the middle of the 12th thoracic vertebra to the lower third of the third lumbar vertebra; about 50 per cent of the cases ended a little above or below the intervertebral disc between 1st and 2nd lumbar vertebrae. The termination in females was found to be at a lower level than in males; Negroes lower than Whites.

MATERIAL AND METHOD

The present work is based on observations made on 72 dead bodies of adults in Punjabi males, at the Medical College, Amritsar. Previous workers based their observations on the results they obtained after dissecting; but in the present series both dissection and roentgenography were employed. The spinal cord was exposed by laminectomy and incision of the membranes. The level of emergence of the coccygeal nerve was taken as the level of the termination. Here according to microscopic studies by Tailor (1938), Harmeier[7] (1933), Needles[3] (1935). spinal grey matter almost totally disappears.

In 50 of our cases roentgenographic technique was followed; in this a metalic pin was transfixed at the level of emergence of the last coccygeal nerve and an antero-posterior roentgenogram was taken to establish its relation to a vertebral body or the intervertebral disc Fig. 1. In another 22 cases relation was established by vision to a third of a vertebra or to an intervertebral disc.

---

* Anatomy Department, Medical College, Amritsar.

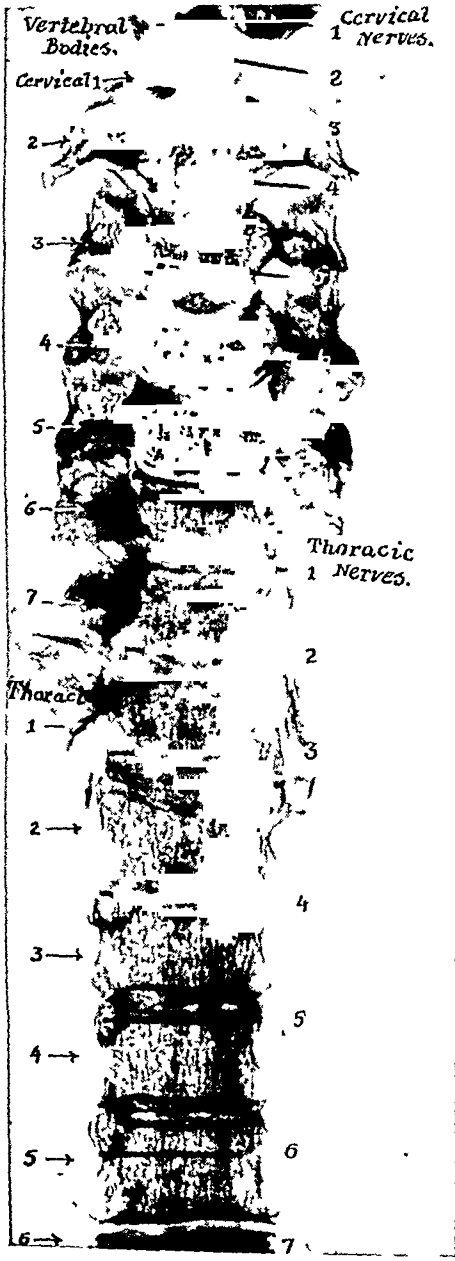

Vertebral Bodies.
Cervical 1
2
3
4
5
6
7
Thoracic
1
2
3
4
5
6
Cervical Nerves.
1
2
3
4
Thoracic 1 Nerves.
2
3
4
5
6
7

Fig 1.

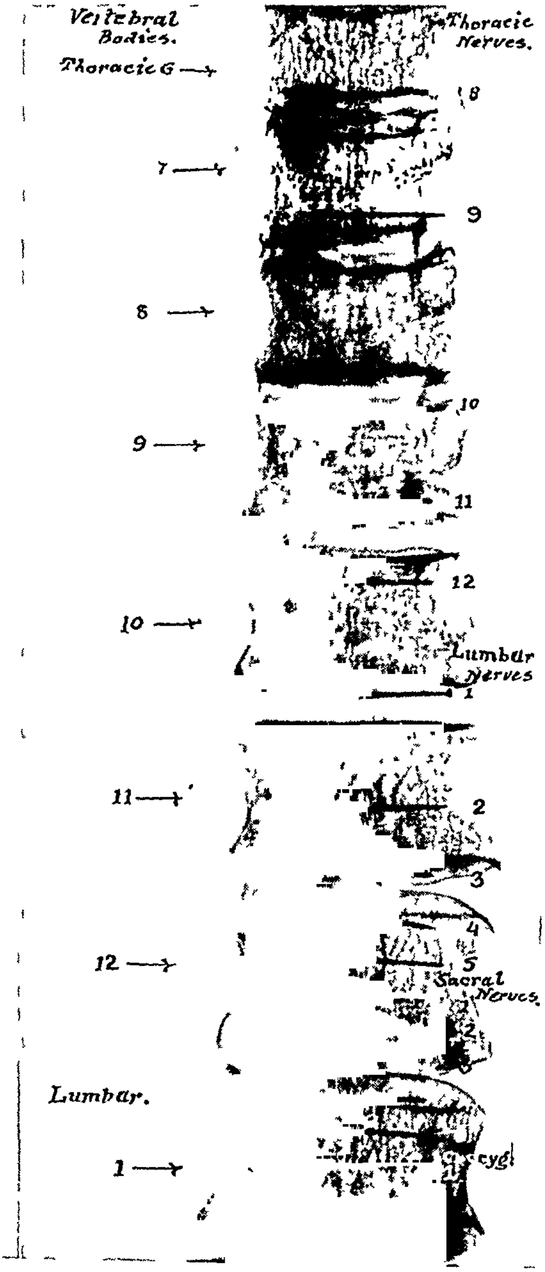

Vertebral Bodies.
Thoracic 6
7
8
9
10
11
12
Lumbar.
1
Thoracic Nerves.
8
9
10
11
12
Lumbar Nerves
1
2
3
4
5
Sacral Nerves.
2
Coccygl

Fig 2

TABLE I—*Showing comparison of level of termination of the spinal cord between the present series and others reported.*

Vertebral Thirds.			Present series.		Reimann.		Needles.		McCotter.		Thompson.		Reid.	
			No.	Percentage.	No.	Percentage.	No.	Percentage.	No.	Percentage.	No.	Percentage.	No.	Percentage.
T	12	Middle	..	..	..	..	2	0.83	..	..	1	0.5	3	0.3
		Lower	..	..	5	3.9	12	5.0	3	0.9	2	1.01	22	2.5
L	1	Upper	6	8.3	13	10.0	20	8.3	19	6.7	12	6.1	70	8.0
		Middle	4	5.5	15	11.6	17	7.1	35	15.2	26	13.1	97	11.1
		Lower	26	36.1	31	24.0	58	24.2	64	28.1	74	37.4	253	29.4
L	2	Upper	20	27.7	25	19.4	61	25.4	48	20.5	49	24.7	203	23.2
		Middle	10	13.9	23	17.8	36	15.0	30	13.4	17	8.6	116	13.3
		Lower	6	8.3	14	10.8	26	10.4	31	13.9	16	8.1	93	10.6
L	3	Upper	..	..	2	1.5	5	2.1	4	1.4	1	0.5	12	1.3
		Middle	..	..	1	0.8	2	0.8	..	..	..	..	3	0.3
		Lower	..	..	..	..	1	0.4	..	..	..	..	1	0.09
		Total	72	..	129	..	240	..	234	..	198	..	873	..

OBSERVATIONS AND DISCUSSION

In the current series, termination of the spinal cord ranges from the level of the upper border of the first lumbar vertebra to the lower third of the second lumbar vertebra. The variation in the level of termination observed is markedly less than that reported by Needles[3] Reiman and Anson.[5] With the segments included between the lower third of the first lumbar vertebra and the upper third of the second lumbar vertebra 63.9 per cent of the total number are included, 83.3 per cent were included between the middle thirds of first and second lumbar vertebrae.

Comparing the present set with the others reported, a total of 873 records are brought into a common system in Table 1. The scheme adopted by Needles[3] is employed, in which each vertebra is divided into thirds, the neighbouring half of the intervertebral disc being included with its adjacent upper or lower third of the vertebra.

When the data was so arranged it was found that within the limits of the lower third of first lumbar and the upper third of second lumbar vertebra,the spinal cord terminated in 63.9 per cent of the current series, 49.6 per cent of Needles[3], 48.6 per cent of McCotters[2], 62.1 per cent of Thompsn[6] or 56.05 per cent of the combined sets.

CONCLUSIONS AND SUMMARY

1. In the present investigation both roentgenographic and dissection methods were employed.

We consider that the roentgenographic method is a more accurate way of determining the level of termination of spinal cord.

3. The present series of 72 adult male specimens show a range of variation in termination of the spinal cord from the upper border of first lumbar to the lower third of second lumbar. The average level is opposite the disc between the first and the second lumbar vertebra. All cases in the current series terminated within the teritory of the upper two lumbar vertebrae.

4. A compilation of 801 similar records from the literature shows a range from the middle of twelfth thoracic to the lower third of the third lumbar vertebra. One case where the spinal cord ended at the level of the third sacral vertebra has been mentioned by Reiman.[5]

REFERENCES

1. Harmeier, J.W.: The normal histology of the intradural filum terminale, Arch. Neurol and Psychiat. 29: 308-315, 1933.

2. Mc Cotter, R.E.: Regarding the length and extent of the human medulla spinalis, Anat. Rec., 26: 559-564, 1916.

3. Needles, J.H.: The caudal level of termination of the spinal cord in whites and negroes. Anat. Rec., 68: 417-425, 1935.

4. Reid, R.W.: The relations between the superficial origins of the spinal nerves from the spinal cord and the spinous processes of the vertebrae. J. Anat and Physiol, 23: 343-353, 1889.

5. Reimann, F. and Anson, J.B.: Vertebral level of termination of the spinal cord with report of sacral cord, 88: 127, 1944.

6. Thompson, A.: Fifth Annual Report of the Committee of the Anatomical Society of Great Britain and Ireland for the year 1893-1894. J. Anat. and Physiol, 29: 46, 1894.

THE ASSOCIATION OF PHYSICIANS OF INDIA

ANNUAL CONFERENCE 1951

PRESIDENTIAL ADDRESS

DR. P. KUTUMBIAH, M.D.

"THE FUTURE OF MODERN MEDICINE IN INDIA"

Modern medicine has been flourishing in India for over two centuries and it cannot be asserted that it has accomplished in India what it is capable of accomplishing and has accomplished in other civilized countries of the world. The medical sciences are today giving the world the healthiest period it had ever known. With the help of the discoveries of the modern medical sciences plague, leprosy, small-pox, intermittent and remittent fevers, dysenteries and cholera, have been banished from all civilized countries. In India these diseases still ravage and take a heavy toll of human life. It is evident that this state of affairs cannot be attributed to modern medical science but to the imperfection and inadequacy of the existing medical service in India to fully utilise the discoveries of modern medical science in the fields of prevention of diseases. The problem that confronts those who are in charge of the National Health is that medical service should eventually provide everything that modern medical science can offer towards the preservation of health and the cure of diseases and that it should make available their benefits to the entire population. It is admitted that medical science in India is not at present optimally organised and supervised and distributed but also that the development of plans for its improvement should be preceded by the inclusive study of the many complex factors involved and should not be directed towards the support of any preconceived scheme which has not been based upon such theory.

The Government of India have been conscious of the urgent necessity for the improvement of the existing medical service so that its benefits may be made available to the entire population of India. With this object in view they appointed the Health Survey and Development Committee to make an inclusive survey of the many complex factors involved and advise them as to the steps to be taken to achieve this end. After a comprehensive survey of the many complex factors involved the Committee has drawn up a Health Programme in two parts, one a programme for the somewhat distant future and the other a short term scheme covering two five-year periods. The attainment of this objective, which may take about forty years, is to be achieved through successive stages of intensive effort directed towards the production of the necessary trained personnel and the creation and development of the organisations and institutions which will form essential parts of the community's health service. The future of modern medicine in India will depend entirely how far the Government is able to implement their recommendations in the orderly manner suggested and the co-operation which the Government receives from the public of this country. Without the mutual co-operation of the Government and the people it is futile to hope that anything substantial can be accomplished.

The main problem which underlies the success of the recommendations of the Health Survey and Development Committee is the supply of medical men in the required numbers and of the right quality. The utter inadequacy of the available number of medical men for the task to be accomplished is vividly realised. But in the attempt to produce medical men rapidly to meet the demand there is a danger of sacrificing quality. The quality of the medical men turned out of our medical colleges will depend on the nature of the medical education imparted to the students in these institutions. This raises the question of the present status of our medical education. Modern medical science is the product of a long evolution. Starting as an art modern medicine has slowly emerged as a science in the course of a few centuries. As Clifford Allbutt remarks "The beginning of the 20th century saw the emergence of medicine from an art of observation and empericism to an applied science founded upon research; from a craft of tradition and sagacity to an applied science of analysis and law; from a descriptive code of surface phenomena to the discovery of deeper affinities; from a set of rules and axioms of quality to measurements of quantity." Medicine is not a mere applied science but a science in its own right. It is an independent form of scientific activity. It is capable of being pursued and developed as such and is on equal terms with the other sciences. The scientific element in medicine is not merely applied physiology and applied pathology. While taking full advantage of any appropriate discoveries in the ancillary sciences of physiology and pathology it need no more wait on the advance of these sciences but is bound to undertake physiological and pathological researches of its own when they become relevant to its purpose. Medicine at the beginning of the 20th century has become largely an experimental science. In recent times it has become a fashion to deprecate the art of medicine at the expense of the scientific aspect of medicine. This attitude is not justified. The art of medicine will long remain the chief implement of the practical doctor. It still forms the back bone of medical practice and is indispensable to mankind. The art and the science of medicine represent the two great activities of medicine. The art of medicine ministers to the immediate needs of sick individuals and may be called curative medicine. The science of medicine is concerned with the advance of medical knowledge and may be called progressive medicine. The modern medical student must be trained in both these aspects of medical science—the curative and progressive.

Our medical colleges are at present so constituted that the greatest emphasis is laid on curative medicine. Our graduates are trained to diagnose diseases and effectively treat these cases according to the best traditions of modern medicine. The progressive side of medicine is very much neglected and very meagrely provided for with the result we are not building up a reserve of well trained and qualified men who will whole-heartedly devote all their time to progressive medicine. Progressive medicine requires the organisation in the colleges of well equipped laboratories where all available facilities for research is provided and men who have chosen research as their career are in charge of these laboratories. A survey of our medical colleges reveals the weaknss of our training of medical graduates in the science of medicine. The fundamental subjects like anatomy, physiology, biochemistry and pathology are very much neglected. There is not at present available enough professors of knowledge and accomplishment to fill these important chairs in our colleges and hence they are filled with any available candidate with the minimum of qualifications. In the last one decade every possible opportunity has been utilised to train men in medicine and its allied branches and surgery and its allied branches. There has been no attempt to choose young men of brilliance and promise and attract them to the vital subjects of anatomy, physiology, biochemistry and pathology. Particularly it is deplorable to see the lack of eminent physiologists in our medical colleges. Unless the Government embark on a far sighted scheme of attracting young men of promise to these departments the future of modern medicine will be very gloomy indeed in India.

"The final and practical use of all medical science is to maintain health and to combat disease in mankind. It is in the very nature of things that the study of disease, to be effective, must begin as it must end, with disease itself, and that all knowledge applicable to human disease must owe its inspiration directly or indirectly, to intimate contact with disease as this exists in living man. If the vitality of medicine is to be increased, it must be clearly recognised that there is a fertile science that deals primarily with patients, and this must be encouraged to a more vigorous growth. This science may be-termed experimental medicine or clinical science. This science seeks, by observation and otherwise, to define diseases as these occur in man; it attempts to understand these diseases and their many manifestations, and here especially makes frequent use of the experimental method. It makes definite experiments upon disease or watches the effects of experiment conducted by injuries, however these arise; it culls, or actually creates, and uses physiological and pathological knowledge immediately related and applicable to the diseases studied. The work of clinical science cannot be delegated to laboratories. It must be inspired and sustained by direct contact with disease. It must be carried through in a very large measure by observations on sick people." For this purpose it is essential that in every medical college a research Professorship should be established and all facilities for research work in this experimental medicine should be provided. I must refer in this connection to the pioneering work done by the Indian Council of Medical Research. It has a very important section connected with clinical research. In the past few years the Council have tried their best to stimulate research in clinical science and by awarding research scholarships have sought to promote experimental medicine in medical colleges. But this is not enough. The various medical colleges must rise to the occasion and provide for these research scholars suitable places where their research could be conducted. This would mean a reorganisation of our departments of physiology, biochemistry and pathology in our colleges. There is a wrong impression that research has no relation to the practice of medicine and it concerns only people working in the laboratories. While it is true that the practising physician or surgeon cannot be expected to be in touch with the work of research carried out in the laboratories, it is imperative that they should in their practice utilise the knowledge gleaned by the research scholars in their laboratories. As Clifford Allbut remarks "Research is the salt of the most practical training. It cannot begin too soon. It is the light of the wisdom of man, the mind of the boy, and the heart of the child. Education has so long lingered on Hellenistic and Scholastic ways, on the systems of abstract notions unvexed by verification, that the hard-shell practical man is still occupied by the notions of antiquated theory, and the phrases of a dead or moribund nosology. The majority of medical men have to work upon the store of scientific ideas and facts with which they set out in practice; onwards they may gain in adaptiveness and technical facility; but can dig little deeper into the strata of knowledge; but for the modern academic spirit this would spell, as in history it has spelled, stagnation. Therefore it is of the greater importance that every student should start on his career well equipped with scientific principles. If, thus equipped, he be not at first so handy a doctor as his seniors, yet with his larger mental grip he will soon pick up common devices and apply them with more freedom and economy."

Once the main problem of the production of well qualified well trained and well equipped medical men is taken on hand, the next problem that has to be tackled would be the organisation of the medical service in this country to provide the most effective medical service for the rural areas of India. The great importance of this problem is realised by all medical men and the Government of the country. The Prime Minister has emphasised this problem on many occasions. "The health of the villages requires special attention. The country derived its vitality from the villages. It is not enough for large imposing hospitals and other buildings to be put up in the towns; the benefits of health must be extended to the whole countryside " As noted above the Health Survey and Development Committee have taken the countryside as the focal point of their main recommendations because they realised the basic problem before the country was the provision of adequate health protection to the people living in the rural areas.

How to provide the most effective medical service for rural India poses not one but many problems—problems centering about the essential characteristics of the rural areas and their relation to the medical service deficiencies. "In varying combination and degree poverty, isolation and ignorance account for the lack of medical services in many rural areas, for the poor quality of much of the medical services now available, for the scarcity of good hospitals, for the persistence of diseases which modern medicine can prevent or cure, and for the relatively high maternal and infant death rates. Paradoxically enough, advances in medical science itself also account in large measure for certain of the deficiencies in rural medicine. Far-reaching changes in techniques of diagnosis and therapy during the past quarter-century have caused well trained doctors to concentrate in cities because of their demand for access to good hospital facilities, easy reference to specialists, and ample opportunity to gain in knowledge and experience by association with other members of their profession. Isolation, perhaps as much as poverty, has delayed educational progress in rural areas. Inferior education, in turn, is responsible for ignorance, in this country even illiteracy and ignorance has been at the root of some of the farmers' troubles. There are farmers whose attitude toward personal hygiene and medical services are those which were common among the mass of the population fifty or even a hundred years ago. Many follow a heavy and unhealthy diet, and are not apt to enquire into the source of the water they drink. Becoming ill they are likely to dose themselves and waste their money on patent medicines. Last but not least, there is still current in rural communities the older notion that a hospital is a place to be avoided, and partly as a result, even the few hospital beds available are frequently unoccupied." This admirable summary of the characteristics of rural America, applies in toto and even with greater force to rural India.

In the light of the difficulties involved in any attempt to extend and improve medical care in the most needy areas of rural India many steps must be taken. This task will require many years for its achievement and it can be accomplished only step by step and in a cumulative and accelerating fashion. There is no room here for any shortcuts or any improvisations. The immediate objective must be the five year programme recommended by the Health Survey and Development Committee and a start must be made with the creation of the primary health centres suggested in that report and make it attractive and workable. If the Government feel that they are unable to start this scheme due to financial stringency then an attempt must be made to start it in a modest way. A good public health service is the first essential today in many areas of rural India where poverty, isolation and ignorance preiail. There is already in some States a well organised public health department staffed with qualified and experienced personnel. This department must undertake the pioneer work in teaching the populace the elements of personal hygiene, nutrition, and preventive health measures. Progress will be slow at first for the public health personnel will have to check water supplies and sewage disposal, immunize children against contagious disease, provide pre-natal care, as well as, instruction in infant care for mothers and carry on a vigorous anti-venereal disease campaign and other related functions. That an energetic and well conceived public health programme can drastically reduce infant, child, and maternal morality, as well as, the incidence of communicable disease has been demonstrated many times over. There are already District Health Officers who are carrying on this work on a modest scale in each district. The personnel of the staff of District Health Officers must be appropriately increased and supplemented by such elements as are not present in the present set up. The present quota of sanitary inspectors must be greatly increased and their training extended and intensified so as to include the above mentioned public health subjects. By doubling or trebling the present recruitment of sanitary inspectors and giving them the above suggested instruction a great move forward will be made. An intensive training for a period of 12 months ought to suffice for this purpose. Nurses, and midwives for maternity and child welfare work must also be added to the staff. Squads of well trained and well equipped workers to carry on the work of D.D.T. spraying and to attend to anti-malarial work must also be created, if they are not already in existence, and attached to the staff of the District Health Officer.

The next important item is the securing of physicians to work in the rural areas. Hospitals and health centres are neither built or staffed in a day. The Achilles heel of medical service is the concentration of qualified medical men in town. "The practice of medicine is both a science and an art and rare indeed is the doctor who can maintain the high standards he acquired in medical college and teaching hospital under the physical, economic, and educational limitations of the isolated rural community." On account of this tendency for doctors to congregate in towns there has been a steady decline of country doctors, a phenomenon not peculiar to India by any means, as it has been also observed in America and England. The reason for this is that good doctors are not satisfied merely to earn a livelihood. They seek to practice medicine according to the high standards they have learnt in their college and for this they require facilities for diagnosis and therapy that are now to be found for the most part in urban areas. The first step in the dispersal of qualified doctors from towns to rural areas is the creation of hospitals in selected places which will afford young doctors good hospital facilities, easy access to specialists, and ample opportunity to gain in knowledge and experience by association with other members of their profession. As a first step in the dispersal of young qualified doctors of the existing District headquarters hospitals must be enlarged and equipped so as to accomodate 200 beds—60 beds for surgery, 60 beds for medicine, 30 for obstetrics and gynæcology and 50 beds for the specialities—ophthalmology, ear, nose and throat, venereology etc. The surgical beds will include few beds for orthopædics and the medical beds few for pediatrics. It is very essential to post these hospitals qualified medical men with ample experience in their specialities to be in charge of their specialities. These hospitals must be provided with X-ray units—diagnostics and therapeutics, well equipped pathology and bacteriology laboratories for serological diagnosis, and when available a dental department. Most important is that these hospitals should run very efficient out-patient departments. The pathology and bacteriology laboratories can be run very efficiently by trained technicians under the direction of specialists. The basic idea is to start as many as possible complete hospital units which will attract young qualified doctors, to pursue their post graduate education and gather experience in medicine, surgery, and obstetrics. As the supply of qualified doctors become available these hospitals may be expanded to accommodate 300 beds. The existing practice of posting the District Medical Officer on the basis of seniority must be abandoned forthwith. The D.M.O. may be utilised for organisation work. Better still nonmedical men with executive experience should be placed in the administrative charge of these hospitals so that the specialists may be free to devote their energies to their professional work. The next expansion when medical personnel become available is to improve Taluk hospitals to accommodate 100 beds. Till these are started the District Headquarter hospitals must be made the centres of village medical work. For this purpose the starting of mobile clinics are suggested. They can bring medical help to a radius of 30 miles centering from the hospital. One well equipped ambulance is enough to start with. A separate personnel must be maintained for this purpose. Two qualified doctors, one or two nurses, one midwife one compounder and one or two dressers will be needed on this unit. Such mobile units are doing yeomen service round about Vellore villages. To begin with, the public health personnel will be resident or easily available to these villages. Mobile clinics can bring enormous benefit to people in particularly isolated areas. Operated wither by the district hospitals or as an adjunct of the public health service, they would be especially useful for maternal and infant care and immunisation programmes and in providing periodic dental care. A service of this sort can also be of value in educating the rural population on the fundamentals of hygiene and nutrition. Equipped with a small screen and a mechanism for sound reproduction the "clinica on wheels" could bring to rural areas otherwise cut off from educational contacts, talks and demonstrations produced for mass distribution by state and federal health agencies or by the staff of regional hospitals. This has been the experience of Rural America. This has also been the experience of Vellore hospital. Dentists are not available at present but in all other respects this example from America can be copied with immense benefit to rural India.

A third and a most important problem on which the future of modern medicine in India will depend is the attitude of the Government and the people towards the claims of indigenous systems of medicine in India. For some years past an agitation has been set on foot to rehabilitate the indigenous systems of medicine on which the future national health schemes should be based. The Health Survey and Development Committee in their recommendations made the following remarks. With regard to the indigenous systems of medicine, the Committee affirmed quite definitely, that there are certain aspects of health protection which in its opinion can be secured wholly, or at any rate largely, only through the scientific system of medicine. Public health or preventive medicine which must play an essential part in the future of medical organisation, is not within the purview of the indigenous system of medical treatment as they obtain at present. The indigenous systems of medical treatment do not at present deal with such vital aspects of medicine as obstetrics, gynæcology, advanced surgery and some of the specialities. Further no system of medical treatment which is static in conception and practice and does not keep pace with the discoveries and researches of the scientific workers the world over can hope to give the best available ministration to those who seek its aid. I entirely agree with the conclusion of the Health Survey and Development Committee that no justification is needed in confining its proposal to the country-wide extension of a system of medicine which must be regarded neither Eastern nor Western but as a corpus of scientific knowledge and practice belonging to the whole world and to which every country has made its contribution. I should like to quote the remarks of a very learned scholar Chandra Chakraberty on Indian medicine in his book "The Ancient Hindu Medicine." "I suffer from no national hypnotism or megalomania. It is very likely that some of my interpretations may not find ready acceptance in many orthodox quarters. But sooner it is realised, it will be better for the communal health that the ancient medical works cannot serve us today any other useful purpose than to supply rich materials for the cultural history of the race. Its prolific vocabulary might be also profitably utilised to create a national school of medicine, for continuity of historic consciousness, activates and acts as a stimulus for progress. Our very great achievements in the past, which we have every reason to be proud of instead of inspiring us with the greatest efforts to lead in arts and sciences, should not mortgage our future to the dead past. For a race that does not take the utmost care and the most advanced methods for the prevention of disease and the preservation of health, cannot effectively compete in the struggle for existence with more forward races and succeed in the survival of the fittest. Health is the foundation of all wealth and progress. We cannot afford to cling to an empty shell, carry the dead weight of the past on our back sacrificing our future, unless we want to be counted with the extinct races."

A study of the evolution of the modern science of medicine reveals many of the fallacies which underlie the present agitation for the revival of the indigenous systems of medicine.

1. A science of medicine based on 'philosophic' and not on "scientific" hypothesis fails to evolve. The medical theories of the

ancient Hindus were based on a priory philosophical concepts, like the panchabhuta theory, and the tridosha theory, which have never been replaced by an accurate knowledge of the function and the structure of the human body. In the days of the first attempts at medical organisation they were legitimate because positive discoveries were few and unimportant. The evolution of the modern science of medicine commenced only after its abandonment of the a priory philosophical concepts of Greek medicine for accurate knowledge supplied by the science of anatomy and physiology.

2. The decay of a medical science is essentially an internal phenomenon. It is sometimes alleged that the invasions of the Mohammedans and take of the British are factors in the decay of the ancient Hindu Medicine. The first may account for the gains made by the ancient Hindu Medicine being lost but it cannot account for the decay of Hindu Medical science. Science was in fact in headlong decay before the sixth century A.D. i.e. before the advent of the Mohammedans. Hindu medical science was not filled, it died. It had reached the limit of possible expansion within the mould in which it was cast. The same fate overtook Greek medicine in the middle ages but the European Renaissance liberated it from the unyielding mould it was cast in and made it flow into the more congenial and elastic mould of scientific medicine. In India historically no such renaissance occurred and Hindu medicine was left in its original mould to perish. Modern medicine is the evolutionary product of ancient Greek medicine. All talk of revival of and research in ancient Hindu medicine is a waste of time as this experiment has been conducted in history on Greek medicine, an ancient medicine very closely allied to Hindu medicine, and this has resulted in the emergence of modern rational medicine. It is wisdom to take the modern rational medicine and to enrich it with our own distinctive contributions rather than repeat the same historical experiment and arrive at an identical result few centuries after.

3. Science can exist and advance only so long as scientific spirit survives. The survival of scientific spirit is dependent on advancing civilisation. The same is true of the science of medicine. Rational medicine is a development of civilisation which better than any other, measures man's intellectual advancement. In the middle ages European civilisation slumped very badly and medicine ceased to be a science and became a matter of salves, poultices, talismans, and spells. The high water mark of ancient Hindu medicine was in the reign of Emperor Asoka. Practically no important addition was made to the corpus of Hindu medical knowledge after that date. In the fifth century A.D. a great renaissance occurred in the reign of

Vikramaditya and after that date Hindu civilisation began to deteriorate and with it Hindu Medical Science also. The great advance made in the European civilisation is entirely due to the fact that the European nations made science the basis of their civilisation and fostered scientific spirit in their peoples. India is still hesitating to take this momentous step and until it is done and the outlook of the present generation is made scientific and scientific spirit is actively fostered in her people, no real advance in the science of medicine can occur in India.

There is a sober appreciation among the advocates of the indigenous medicine of the obvious inadequacy of the ancient surgery. The art of surgery is not of any use to patients without anæsthesia, hæmostasis and asepsis. The science of surgery is only possible with an accurate knowledge of human anatomy and physiology. Without the phenomenal advances made in the sciences of anatomy and physiology in the recent years such highly specialised branches of surgery—the abdominal, thoracic and neurosurgeries—could never have come into existence. It is true that the ancient Hindu possessed considerable skill in surgery but to argue that their surgery could be revived under the present conditions and would serve any useful purpose is to be totally ignorant of the demands of modern surgery.

A great deal of capital has been made about the alleged excellence of the ancient Hindu therapeutics. But here too a study of the evolution of the modern science of therapeutics will help to dispel many of the misconceptions and exaggerated ideas entertained by the advocates of ancient Hindu medicine on this subject. The methods used in the treatment of diseases comprise three basic measures—faith healing, hygienic therapy, and drugs cures. What has a bearing on our discussion is drug therapy. The ancient pharmacopeia was composed entirely of remedies of plant origin, the so called galenicals, after the great Galen. Many considerations weighed in the choice of drugs. The most important one was their recommendation by some one who had used them or heard of their use. Another recommendation was their appeal to the imagination for the healing virtues they were believed to possess. Paracelsus initiated a new approach to the study of therapeutics by introducing certain metals (non-galenicals) into the pharmacopeia. He used and popularised inorganic substances such as mercury, lead, iron, arsenic antimony, copper sulphate, and potassium sulphate as remedies. It is true that some of these had been used long before his time, but had not been generally accepted as useful agents for the treatment of diseases. He is thus the founder of chemotherapy, for he maintained that there was a specific for every disease and that chemistry was the agency for obtaining these specifics. In the twentieth century his belief was revived in scientific form by Ehrlich. The development of the science of bacteriology, particularly through the pioneer investigations of Pasteur, Koch, and their immediate followers between the years 1855 and 1900. Chemotherapy is still an infant science but already it has revolutionised the treatment of infectious diseases. The future of modern therapeutics lies in orderly development of this science.

The pharmacopeia of the ancient Hindus is loaded with a mass of useless remedies that had been collected over many centuries, along with some of proved value. Ancient Hindu medical practice was established by Atreya in the sixth century B.C., did not include an extensive use of drugs. It relied mainly on hygienic therapy and dietetics. Later on a more extensive use of drugs was grafted on the old system. At first the drugs were mainly of vegetable origin but few minerals like mercury were later incorporated. The ancient Hindu medical men lacked an effective method of determining the curative value of drugs. They had to search here and there, blindly trying one preparation after another hoping always that this decoction or that infusion would possess healing power. In early times the difficulties in evaluating the virtues of one or other remedy was enormous, since differentiation of the specific nature of the various infectious diseases had not been made. The method of blind testing was the only one available. The method of 'control' observations and of 'scientific testing of drugs did not come into use in India until the beginning of the twentieth century. When these methods were finally applied, the mass of useless remedies that had been collected over many centuries was slowly discarded and those that were of real value were discovered and these have incorporated into the modern pharmacopeia, which contains many specifics which the modern medical science did not discover. Modern rational medicine does not rely very much on galenicals. It relies mainly on hygienic therapy but is assisted by a moderate use of some well tested and tried drugs. The plea to revive the indigenous systems of medicine for the sake of a few specific remedies is a very short sighted one, as these can be incorporated into the modern pharmacopeia after being scientifically tested. With the growth of the modern science of chemotherapy and the discovery of antibiotics like penicillin, streptomycin, chloromycetin and aureomycin, etc. ancient pharmacopeias have lost much of their importance and charm. Therapeutics divorced from a true science of medicine tends to be purely emperical and in the long run proves sterile.

"Science has made the modern world what it is to-day. Science has entered into every area of our private and public, national and international life. It has enriched us beyond measure, but in that very process it has complicated life—complicated it to the point when it is uncertain whteher we can cope with all that has been thrust into our hands." One of the root problems of our times is the problem of the proper use of science. All the nations of the world, are feverishly planning to utilise the rich dower with which science has endowed them for the reconstruction of the post-war world particularly national health. Everywhere in the civilised world the affiliation of science with politics is noticeable. In India one sees the unfortunate affiliation of politics with science which is proving a serious hindrance to progress. This is particularly the case with the medical science. The ancient Hindu medicine has not been killed, as it is loudly but ignorantly proclaimed by the advocates of the indigenous systems of medicine. It died a natural death. Instead of giving it a decent burial politicians are wasting the nations' time and money in a frantic attempt to revive it and thus put the clock of progress back a few centuries. "The medical sciences are today giving the world the healthiest period it has ever known but they are not yet mature. What has already been accomplished in scientific medicine is small in comparison with the future possibilities of preventing diseases, and alleviatng suffering and prolonging human life. But there is no assurance that these possibilities will ever be realised. In this matter man literally controls his own destiny. The danger to the scientific spirit, to the advance of medicine and to the integrity of civilisation does not come from the mass of unthinking people. This danger comes from the intelligent people in whom the primitive instinct escapes from repression and rises to prevent thought." It is the duty of those who control the destiny of the nation not to be stampeded by this ill-conceived agitation but with vision and courage to go forward and implement the national health programme which after prodigious labour and deliberation the Bhore Committee has prepared for use of the nation.

THE ASSOCIATION OF SURGEONS OF INDIA

TWELFTH ANNUAL CONFERENCE 1951

Impressions by a Correspondent

To the cold northern Capital City of Delhi came over a hundred delegates, for the twelfth Annual Conference of the Association of Surgeons of India.

If the city was cold, the reception accorded to the delegates was traditionally warm. The arrangements made for receiving and accomodating the delegates were thorough, and in a City known for the uncertainties of its transport system, no one could have felt anything but gratitude for the manner in which the organisers smoothed over the difficulties.

The Conference was inaugurated on the 30th December, 1950 by Pandit Nehru. Rajkumari Amrit Kaur, Health Minister, in welcoming the guests, dealt with the great advances that medical science and especially surgery, had made in the last two decades. She spoke of the efforts that had been made to bring these advances to the common people, and of the difficulties that surrounded the fulfillment of this ideal. She made a plea for the cultivation of an outlook of service, and reminded her listeners of the allegiance that they owed to the high principles enshrined in the Hippocratic Oath. Pandit Nehru in an obviously unprepared speech characterised by a certain acid humour, said that major preoccupations like food and foreign policy had relegated national health to a secondary place in the Government's schemes for the betterment of the country. He dealt at some length with the rival systems of medicine that were struggling for dominance in the country, and said that emphasis should be laid not on this or that system being cheap, but on a particular system being efficacious. After all, as he drily remarked, for an overpopulated country like India, there is nothing cheaper than death.

The president of the Association, Dr. Narasimhan, who is well known for his sober scholarship and his devotion to the highest ideals, in a characteristically studious speech, covered a vast field which included not only the history of Surgery in ancient India, but the problem of medical relief and undergraduate and post-graduate teaching. He stressed particularly the role the Association might play in encouraging the development of specialities in the country.

The scientific session was opened with a paper by Dr. R. Mahadevan of Madras on Bronchiectasis and by Dr. S. J. Mehta of Bombay, who spoke on the surgery of lung abscess. The first speaker covered the subject in a comprehensive manner, but unfortunately, no figures of personal mortality rates or cures were mentioned.

Dr. S. J. Mehta showed an extremely high incidence of lung abscess following tonsillectomy performed both under local and general anaesthesia. In cases that failed to respond to therapy with the antibiotics and postural drainage, both open drainage and pulmonary resections, had been resorted to, with good results.

The second afternoon was taken up with a paper by Dr. R. A. Irani and Dr. A. E. de Sa of Bombay, on the subject of intestinal obstruction in children.

In a carefully thought out paper, the speakers produced an impressive series of personal cases, though their mortality figures did not compare at all favourably with those of some of the specialised clinics in Europe or America. They had many original observations to make, from a clinical and operative point of view, particularly in connection with imperforate anus and intussusception.

It was a pity that obvious financial and laboratory handicaps had stood in the way of this paper being a really substantial contribution to the understanding of childhood obstruction.

The third day's session was devoted to the Sciatic Syndrome. Dr. V. P. Mehta of Bombay and Dr. Santosh Sen of Delhi discussed different aspects of disc prolapse. Dr. Sen produced quite a large series of successfully treated cases of disc prolapse.

Dr. V. P. Mehta made a plea for the adoption of a special operating position, which he described in some detail. The discussions that followed all these papers were lively and on the last day, even acrimonious.

Over and above the main papers, the mornings were taken up with short papers, and out of a large number, those of Dr. M. G. Kini of Bombay and Dr. Balkrishna Rao of Gwalior, stand out in the memory.

In addition, visits to Hospitals were arranged, but it was unfortunate that a wide enough variety of operations had not been arranged for the three days that the conference lasted. This was in strong contrast to the operative fare that had been served up at the previous annual session in Madras.

This is but a bare outline of the scientific aspects of the Conference. As though the dry bones of knowledge were not enough, there were enough lunches and dinners arranged to last a healthy delegate till the next annual Conference. And for those that came from Bombay, the joys of this uninhibited and unprohibited city were sufficient to induce a second visit.

Due meed of praise must be given to the local secretary Dr. Santosh Sen for the general excellence of the fare the delegates were served, and to Dr. U. Mohan Rau the popular secretary of the Association, who in his own quiet way, made the trip to Delhi a memorable one.

CURRENT MEDICAL LITERATURE

MEDICINE

AUREOMYCIN IN THE TREATMENT OF THE COMMON COLD, Hoagland R.J., Deitz E.N.; Myers P.W. Cosand H.C.: New Eng. J. Med. 243: 773-775, 1950. 1 table, 1 figure, 6 references.

A controlled investigation regarding the usefulness of aureomycin was carried out in young healthy male military personnel. 309 patients with head colds were divided into two groups:— 154 treated with aureomycin orally and 155 patients received a yellow capsule as a placebo. Aureomycin was given in the dosage of one capsule (250 mg.) four times a day in early stage and in the late stage two capsules (500 mg.) four times a day. There was no significant difference in the proportion of cures reported by patients with cold receiving aureomycin and those receiving the placebo. There was also no difference between those receiving aureomycin in different doses. Furthermore, essentially the same proportion of patients treated with aureomycin and placebo reported slight or no benefit from either type of treatment.

J. C. Patel.

ATYPICAL PNEUMONIA: Stuart-Harris, C. H.: B. M. J. 2: 1457-1480, 1950, 31 references.

Primary atypical pneumonia is a syndrome of infection of the respiratory tract reproduced by many agents, chiefly of the virus or rickettsial group, and particularly the psittacosis group of viruses. R. burneti, and the influenza viruses. It is characterised by varied symptomatology, by roentgenographic changes of a particular character, and by lack of therapeutic response to the sulphonamides or to penicillin. The author reports two cases, which illustrate most of the points emphasized by the large number of case reports in the literature. The clinical features are those of a benign respiratory tract infection, with cough and sputum, low fever, tachycardia, malaise, headache and an unusual degree of respiratory distress. Physical signs suggest a bronchitis rather than a true consolidation. The roentgenographic changes exceed in degree the clinical findings, and hazy opacities or diffuse mottling may be found contrasting with the denser opacity of bacterial pneumonia. Clinically Q fever is not distinct from other atypical pneumonias, but it is usually accompanied with the onset of pleuritic pain. The diagnosis depends on the total clinical features, but may be aided by cold agglutinin tests in that form of the syndrome of undetermined aetiology. For the differentiation of cases of infection due to a particular agent concerned in the syndrome, laboratory investigations are essential. Penicillin alone or combined with sulphonamides was reputed to have some effect in psittacosis, but not in other groups. With the advent of aureomycin, considerable promises of success are met with in atypical pneumonia of undetermined actiology, in Q fever, and, possibly, in psittacosis.

Eric Coelho.

A CONTROLLED STUDY OF THE TREATMENT OF UPPER RESPIRATORY INFECTION WITH PROPHENPYRIDAMINE (TRIMETON), Hirsh, H.L.: Am. Pract. 2: 32-35, 1951.

Many reports have been published on the efficacy of antihistaminic drugs in the treatment of the common cold. The author selected prophenpyridamine because of the low incidence and mildness of untoward effects. The subjects included in this study were all male inmates of a reformatory and fulfilled the following criteria: 1. They presented nasal symptoms regardless of other respiratory system complaints. 2. The temperature did not exceed 99.4°F. orally. 3. There was no history of any type of allergy. The duration of cold was no criterion for inclusion in the study, but most complained of symptoms for one to three days before treatment was started. None of the subjects were hospitalized and all continued their routine work. The severity of the symptoms and findings were noted before treatment was started and each day thereafter for five days. One examiner was responsible for all the questioning and examination to insure complete uniformity throughout study. The selected inmates were divided into two groups and given packages containing 26 tablets. One group were instructed to take 2 tablets immediately followed by 1 tablet four hourly when awake for 5 days. Each tablet contained 10 mg. of Trimeton. The other group took tablets, identical and similar in number containing lactose. The examiner himself was not aware of the contents of the packages. The patients were examined daily and each was asked his opinion as to whether the therapy was effective in alleviating or controlling his symptoms and if the relief obtained was slight, moderate or great. The author tried Trimeton in 517 cases out of 1008 and came to the conclusion that the antihistamine prophenpyridamine (Trimeton) does not completely cure the common cold but does alleviate some of the symptoms and, in some instances, shortens the course by varying degrees.

Eric Coelho.

HYDROXYSTILBAMIDINE IN THE TREATMENT OF INDIAN KALA-AZAR, Sen Gupta, P.C.: Ind. Med. Gaz. 85: 547-553, 1950. 3 tables, 9 references.

The author reports the use of hydroxystilbamidine in 42 cases of Kala-azar. Of these, 25 patients were ordinary cases that had either not received and specific treatment or had received a few injections of relatively ineffective drugs previously, the rest (17 patients) were resistant cases of Kala-azar that had relapsed after courses of treatment with other specific drugs viz., antimonials and|or aromatic diamidines. The diagnosis of kala-azar was made by the demonstration of the parasite Leishmania donovani and|or Napier's aldehyde test and|or the complement fixation test. The duration of kala-azar in the ordinary cases varied from three months to a little over a year and in the resistant cases from 6 months to 3 years. In all but one case the splenic enlargement was seen from less than 1 inch to 10 inches below the costal margin. The route and the number of injections were varied in different groups of cases in the series. In most cases the drug was administered intramuscularly with a 10 per cent aqueous solution in 2 per cent procaine. For intravenous injection the drug was dissolved in ·25 ml. of 25 per cent solution of glucose. The total number of injections varied from .10 to 26 in the ordinary and from 15 to 35 in the resistant cases. The intramuscular injections were given on consecutive days or alternate days or on two consecutive days followed by a day's interval. The intravenous injections were given on consecutive or on alternate days. The mean relative dose per 100 lb. body weight for the ordinary cases was 2.6 G. with a standard deviation of 0.81 G. and for the resistant cases 3.7x1.4 G. With this line of treatment, Kala-azar was clinically cured in 16 out of 17 of the resistant and in all the ordinary cases. On a follow up of the cases 6 months or more after the completion of treatment, 37 cases could be contacted. Of these, all the 23 ordinary and 11 out of 14 resistant cases of kala-azar were completely cured and 3 resistant cases had a relapse of the conditions. Two of these cases that had relapsed, however, had shorter courses of treatment. These results show that hydroxystilbamidine compares very favourably with, and is as effective as, the older drugs including stilbamidine and has the additional advantage of being free from unpleasant immediate effects and sequelae and is well tolerated intra-muscularly with procaine.

Eric Coelho.

INTRAMUSCULAR HEPARIN, Abrahage, D. J.: B. M. J. 2: 1418-1419, 1950: 3 figures: 2 references.

Heparin is the most efficient and safest anticoagulent in common clinical use so far. This drug necessitates frequent intravenous injections, which are irksome to both patient and doctor. This paper describes trials with the administration of heparin intramuscularly in a concentrated aqueous solution of 25,000 units per cc. in 20 cases at the Institute of Cardiology. All clotting times were determined by the method of Dale and Laidlaw. With this technique the normal clotting time was two and a half to three minutes. In order to establish a criterion for adequate anticoagulation when using this method, 16 normal subjects were given a standard dose of intravenous heparin (100 units per kilogram body weight) and the average delay of clotting at ten minute intervals, was noted. The results showed that a satisfactory blood level existed for one hour after intravenous heparin. The author administered 37,000 units i.e. 1.5 cc. of Heparin intramuscularly as the initial dose followed by 1 cc. after 12 hours. With intramuscular injection, the anticoagulant effect was well maintained and even after twelve hours, the delay of clotting was still adequate when judged by the criterion previously stated. Local pain and occasional haematoma were met with, but can be minimized by simultaneous injection of 1.5 cc. of 1 per cent solution of procaine and the use of 18—20 gauge needles. The intramuscular injection should preferably be given into the vastus lateralis muscles. The results of this trial indicate that this is a satisfactory method for short or long term anticoagulant therapy and can be safely carried out in the home.

Eric Coelho.

POSTASSIUM DEFICIENCY IN PYLORIC STENOSIS, Hawkins, C.F., Hardy, T.L., and Sampson, H.H.: The Lancet 260: 318-321, 1951.

As little attention is being paid to the potassium ion when treating the profound electrolytic disturbances that accompany many gastro-enterological conditions, the authors present a case report of a typical example of hypokalæmia and its dramatic response to specific therapy. The case was an adult aged 47 with advanced pyloric stenosis, who complained of continous vomiting. The loss of hydrochloric acid and water gave rise to hypochloræmia with alkalosis. Finally dehydration with an insufficient glomerular infiltration pressure led to acute renal failure. The condition improved temporarily with glucose-stline infusions, but his apathy, muscular atonia, absent reflexes, bradycardia and shallow respirations, clinically indicated a potassium deficiency. This was confirmed by electrocardiographic findings, and by biochemical evidence which showed a low-serum-potassium level. The authors show that the effect of treating such a patient with large quantities of intravenous sodium chloride is not only to increase any potassium deficit by causing a potassium diuresis, but also to substitute sodium for potassium in the cells, an exchange which is a feature of alkalosis. There seems to be a reciprocal relationship between sodium and potassium, and the giving of generous infusions of sodium chloride as a routine may be ill-advised and even dangerous unless their amount is controlled by frequent serum potassium estimations.

In the present case, the authors did not use the intravenous route because it was not the total dose that was important, but the amount of serum-potassium that reached the heart. The administration of potassium chloride orally has no effect. The authors gave a sub-cutaneous infusion with hyaluronidase and dramatic improvement was noticed with the reversal of electocardiographic abnormalities. The symptoms of hypokalæmia returned when the infusion was stopped, but ultimately the patient recovered fully.

Eric Coelho.

STREPTOMYCIN TREATMENT OF TUBERCULOUS LESIONS OF THE TRACHEA AND BRONCHI—A report to the Medical Research Council by the Streptomycin in Tuberculosis Trials Committee, The Lancet 260: 253-257, 1951. 7 tables, 8 references.

This study covered 35 patients treated in 6 chest hospitals. The patients were admitted to the trial only if they confirmed to three criteria. 1. Ulceration or granulation tissue had to be visible on bronchoscopy. 2. Thd tracheobronchial lesion was to be considered an important factor in the prognosis. 3. The diagnosis was based on the finding of tubercle bacilli in the sputum or on bronchial biopsy. It was not thought practicable to conduct a controlled trial with a parallel series of untreated patients because frequent bronchoscopies in patients who were being treated by rest alone would not have been justifiable. Bronchoscopy was done before treatment was started, and was repeated after two months, and again after four months treatment. Patients were then kept under observation for two months without further streptomycin. In 24 cases bronchoscopy was repeated six months after the commencement of treatment, before discharge. The patients under trial were classified into 5 groups according to their clinical features Group A with 3 patients having no infiltration visible in the chest film, group B with 7 patients having symptoms out of proportion to the small extent of lung disease, group C, 11 patients with persistently positive sputum after apparent control of the lung disease by collapse measures, group D, 4 patients with radiological evidence of bronchial obstruction and group E, 10 patients with tuberculous cavitation. Streptomycin was given intramuscularly 6 hourly, for four months, the first 21 patients receiving 2 Gm. and the rest getting 1 Gm. per day. The results of the treatment was as follows. In 24 of the 35 patients, the bronchial lesion was found to be greatly improved or healed when final bronchoscopy was done, four or six months after treatment. In 15 patients out of 33 who were subjected to bronchoscopy two months after starting treatment, there was considerable improvement in the bronchial lesions. In cases that showed no improvement in the first two months of treatment no benefit was noted with further treatment. The healing of the bronchial lesion was greater in those with limiced lung disease than in those with tuberculous cavities. Bronchial stenosis was present before treatment in 15 patients and in 7 more cases it developed during treatment. In 24 cases, including 2 treated by artificial pneumothorax, 1 by thoracoplasty, and 1 by pneumonectomy, the sputum became negative. In 2 cases, inspite of streptomycin treatment, masses of granulation tissue required removal at repeated bronchoscopies. Although the cases under trial were few, there was a slight suggestion that the lower dosage of streptomycin was less satisfactory.

Eric Coelho.

LINCTUSES, Gordon Sears, W.: The Pract. 166: 91-92, 1951.

Linctuses are viscous liquid preparations containing mostly sucrose and medicinal substances possessing demulcent expectorant or sedative properties. They are prescribed in small doses and should be sipped and swallowed slowly without the addition of water. The usual dose is 60 minims. They are usually administered to allay cough which is troublesome, useless and unproductive and which may be painful or disturbing to the rest and sleep of the patient. Among the common indications for the use of a linctus are: coryza, pharyngitis and laryngitis, the early stages of bronchitis, influenza and pneumonia, dry pleurisy, pulmonary tuberculosos, and new growth of lung. The following linctuses are in the B.P.C. (1949). The approximate amount of morphine, codeine or diamorphine in each 60 minims, has been added after the dosage.

Name.	Dose		Morphine, Codeine or Diamorphine per 60 minims (3.5 cc.)
	Minims	Cubic centimetres	
Compound linctus of chloroform and morphine. ..	30-60	1.8-3.5	1|20 grain (3.2 mg.)
Linctus of codeine, N.F.	30-60	1.8-3.5	1|8 grain (8 mg.)
Linctus of diamorphine.	30-120	1.8-7.0	1|20 grain (3.2 mg.)
Linctus of diamorphine and hyocyamus ..	30-120	1.8-7.0	1|20 grain (3.2 mg.)
Compound camphorated linctus of opium ..	30-60	1.8-3.5	1|150 grain (0.43 mg.)
Linctus of squill .	30-60	1.8-3.5	
Opiate linctus or squill (Gee's linctus) ..	30-60	1.8-3.5	1|100 grain (0.65 mg.)
Simple linctus, N. F. ..	30-60	1.8-3.5	
Opiate linctus of squill for infants, N.F. ..	30-60	1.8-3.5	1|450 grain (0.14 mg.)
Simple linctus for infants, N.F. ..	30-60	1.8-3.5	
Compound linctus of tolu for infants, N.F. ..	30-60	1.8-3.5	

From this table it will be observed, that in addition to their demulcent properties, they contain very small doses of drugs which depress the nervous mechanism of the cough reflex. Diamorphine and heroine are no longer included in the index of the National Formulary as they are habit forming. An equally powerful linctus is 'physeptone (brand) linctus' (B. W. & Co.), a D.D.A. preparation which contains 2 mg. of physeptone in each 60 minims.

Eric Coelho.

SURGERY

RETROGRADE AORTOGRAPHY WITH A SPECIAL CATHETER INCLUDING DEMONSTRATION OF THE CORONARY ARTERIES:

Pearl, F., Gray, N. and Friendman, B.: Annals of Surgery 132: 959, 964, 1950.

Though roentgenographic demonstration of the heart chambers and the great vessels by radio-opaque injection into the venous system is well established the visuarisation of the left side of the heart and thoracic aorta have presented formidable difficulties.

Demonstration of the abdominal aorta by direct translumbar percutaneous puncture necessitates general or spinal anaesthesia and carries the risk of injury to the artery or surrounding structures.

In 1941, Farinas reported the delineation of the abdominal aorta by means of a rubber catheter introduced through a trocar into the femoral artery but later favoured "retrograde abdominal aortography" because of his inability to procure rubber catheters.

Radner used a direct injection into the aortic bulb to visualise the aorta and coronary arteries in dogs. Hoyos and del Campo injected 30 cc. of 70 per cent Diodrast directly into the human aorta through the second left interspace.

Grossman secured proximal aortogram in dogs by means of a wax catheter introduced through the right common carotid which was ligated.

These techniques had the disadvantages of requiring large quantities of radio-opaque medium, unnecessary widespread and non-selective arteriography, and the great force required to inject the solution (except with the catheter method of Grossman) might have damaged or ruptured a weakened arterial wall. One of the authors devised a thin-walled radio-opaque catheter which could be inserted into a peripheral artery and guided to any part of the aorta. The outside diameter (2.50 mm.) is small enough for insertion and may be readily restored by suture.

First used on dogs, the catheter was passed through the femoral or carotid arteries and successful arteriograms of any portion of the aorta were made with small amounts of Diodrast. Satisfactory pictures were obtained of the left ventricle, aortic valves, coronary arteries, proximal aorta, aortic arch and its main branches. By placing the catheter tip at various levels in the descending aorta, the coeliac axis, the mesenteric arteries and renal arteries were demonstrated, showing minute branches in the stomach, liver, spleen, intestine and kidneys.

The authors reported regular demonstration of the coronary arteries with 4 cc. of radio-opaque liquid. Electrocardiograms taken during the passage of the catheter and after injection, showed no abnormality. The catheter has been used only in one human subject just below the brachial bifurcation. The artery was restored by suture and the radial pulse at the wrist promptly returned and persisted.

Technique: A segment of artery is exposed and adventitia stripped from it. The blood flow is temporarily occluded by serrefines. The opening in the artery is made slightly smaller than the diameter of the catheter, which is then gently inserted. It is kept free of blood by connecting it to an apparatus which delivers a few drops per minute of heparinized salt solution at just below systolic pressure. The serrifines are removed and the catheter passed to the desired location. The position is checked by fluoroscopy. The pressure apparatus is replaced by a 50 cc. Robb syringe containing the radio-opaque medium. From 4—10 cc. are sufficient. The solution is injected as quickly as possible. Two roentgen exposures are made about one eight to one fifth second apart, the first about half a second after the injection has begun. The syringe is immediately replaced by the pressure apparatus. If necessary the catheter may be kept for more exposures with different positions or it is removed making sure the artery is free of clots. The opening is closed.

Eustace J. de Souza.

TWO NEW METHODS FOR REDUCING DISCOMFORT AFTER HAEMORRHOIDECTOMY, Heart, D: Am: J. Surg. 81: 31-32, 1951.

Several early perianal epitheliomas were treated with wide incision followed by cauterisation of the exposed area with nitric acid. The excellent anaesthesia obtained post-operatively and the superior healing of these wounds led to the use of nitric acid for this purpose in other rectal operations, e.g. on the skin edges of fistulectomy wounds, and outer skin edges after hæmorrhoidectomy. The author now uses nitric acid as a routine after operations for piles.

Full strength nitric acid is lightly brushed on the skin edges with a firm cotton applicator from which excessive amounts of the acid have been removed by blotting in gauze. Extreme caution must be taken to prevent the acid from coming in contact with the muscle. The use of the technique has not only prevented much post-operative pain but has also checked too rapid healing of the outer part of the wounds and has thus encouraged satisfactory drainage. At no time has more tissue destruction occurred than was desired. However, it is evident that injudicious use of nitric acid could easily cause destruction of too much skin and muscle.

The use of a bulk laxative enema is another method of reducing pain of the first bowel evacuation. The more commonly used oil retention enema or other methods seem to soften the stool so much that its full value is lost and the patient still has to wait in dread for his first spontaneous evacuation. Four or five drams of bulk laxative are quickly mixed in a few ounces of tap water and instilled in the rectum, using a large asepto syringe and a wet No. 22 French catheter. The material is retained and soon becomes partly solidified, usually resulting in a normal evacuation within a few minutes to a few hours. The soft gelatinous mass precedes the more solid fœcal mass and less than the usual discomfort is experienced. It is usually necessary to demonstrate the use of this technique to the nurse or she will not mix and instill the ingredients rapidly enough and solidification will occur in the syringe and catheter.

Other principles that require attention if post-operative gas pain are to be prevented are:— (1) the avoiding of any type of post-operative anal-plug; (2) the use of a small, water enema the night before surgery, instead of the more irritating enemas, and avoiding an enema on the day of the operation, (3) the placing of a piece of gauze in the rectum at the beginning of the operation to prevent blood from running into the sigmoid, the gauze being removed at the end of the procedure.

Fear and apprehension of the patient especially of pain at defæcation must be allayed. Pain is due to muscular spasm and the patient must be taught to relax.

E. J. Borges.

PEDIATRICS

SIGNIFICANCE OF TACHYCARDIA IN CHILDREN, Thomson J.: The Pract. 166: 88-90, 1951.

The term tachycardia means an abnormally rapid heart rate. The normal heart rates at various ages are as follows:

Age	Rate per Minute
Birth	120
6 to 12 months	115-105
2 to 6 years	105-90
7 to 10 years	90-80
11 to 14 years	80-75

The pace-maker of the heart, the sino-auricular node, is controlled by the varying degree of tone of the right vagus, and in the newborn, vagus tone is minimal. It has been suggested that this in turn is due to the low arterial pressure in the newborn and consequently explains that as the blood pressure rises throughout childhood, the cardiac rate falls. This article deals with tachycardia occurring in the absence or virtual absence of pyrexia. This tachycardia may be produced by a diminution in vagal tone, by increased sympathetic action, or by the advent of a new or ectopic pace-maker in the heart.

A compensatory tachycardia is produced in conditions where the myocardium is impaired. This is caused by a diminished cardiac output and lowered blood pressure which depresses the vagal tone. Tachycardia of this type occurs in the post-pyrexial period of a number of infections viz., diphtheria, influenza, and scarlet fever but the most common cause in childhood is rheumatism. Often the onset of tachycardia is insidious and the child is brought because he is pale, easily fatigued, is out of sorts and is not eating well. History of having headaches and perhaps occasional pains in the limbs, or susceptibility to throat infection may be disclosed. In some cases the child complains of abdominal pain which disappears on rest or there may be epistaxis. A physical examination will reveal not only a tachycardia but also some slight enlargement of the area of cardiac dullness; some indistinctness in the heart sounds, and perhaps the presence of a systolic murmur. The tachycardia associated with anxiety states is functional and is due to the overactivity of the sympathetic nervous system. Such children react violently to change in their environment viz., the absence or anticipated absence, of a parent overnight, the anticipation of a journey etc. Unlike rheumatism, attacks of this nature have a fairly sudden onset and are short lived though recurrent. Such children are often lacking confidence. Before making a diagnosis of functional tachycardia, paroxysmal tachycardia and tachycardia due to a hyperthyroid state must be excluded. The tachycardia of hyperthyroidism is by no means uncommon in childhood, especially in girls over the age of 10 years. The onset is gradual. Nervous manifestations are frequent and early symptoms. There is excessive activity and excitability. There is tachycardia. The warm moist skin is accompanied by flushing. The child is emotional and unstable. To distinguish it from functional tachycardia a count of the sleeping child's pulse is invaluable, for the tachycardia of an excitable child will disappear during sleep. It should be remembered that during adolescence the endocrine system undergoes further development and readjustment, and this may cause a physiological enlargement of the thyroid gland with resultant tachycardia.

So far, tachycardia has been considered mainly as an aid in diagnosis. In paroxysmal tachycardia the increased heart rate and its abrupt onset without apparent cause, are the outstanding features of the condition. It may be started by some trigger mechanism or it may be of psychological origin, or it may be associated with nausea and vomiting or may occur in the course of rheumatism or hyperthyroidism. The heart rate is regular and may be anything from 180 to 300 or more beats per minute. The heart is of ectopic origin. The duration of the attack varies, and if prolonged unduly cardiac dilatation ensues with signs of congestive heart failure. This condition is a medical emergency and every effort should be made to terminate the attack. In children, the application of a tight abdominal binder or flexing the trunk so that the head is between the knees, may terminate the attack. The splashing of cold water on the face may prove successful. The older children may be taught deep breathing with expiration against a closed glottis. The production of emesis, mechanically or by the administration of an emetic dose of ipecacuanha, may prove beneficial. A strong pressure over the carotid sinus to produce vagal stimulation may be helpful. Ocular pressure, though painful, yields good results. When these measures fail, and in any case if there are signs of the onset of congestive heart failure, the intravenous injection of mecholyl or doryl may bring about a normal rhythm. These substances are akin to acetylcholine which is the substance released at the parasympathetic nerve ends when such nerves are stimulated. Other appropriate agents are quinidine, digitalis and quinine.

The other less common causes of tachycardia are enlargement of the mediastinal glands, mediastinal fibrosis, intrathoracic neoplasm and aortic aneurysm. These conditions give rise to irritation of the vagus nerve and hence the tachycardia. Anoxia, of any origin, produces tachycardia, thus it is found in an anæmic states and following hæmorrhage. The rarest of all causes is thalamic tumour. The practitioner must bear in mind that certain drugs like belladonna and thyroid gland extracts cause tachycardia.

Eric Coelho.

PSYCHOLOGY

THE INCIDENCE OF CERTAIN VEGETATIVE DISTURBANCES IN RELATION TO PSYCHOSES, Ross, W.D. et al.: Psychosom. Med. 12: 179,1950.

The incidence of certain chronic vegetative disturbances has been determined among 1,600 *patients in* a Canadian mental hospital. The previous literature has been discussed concerning the frequency of the disorders among psychotic patients as compared with the general population.

Peptic ulcer appears to be less common among psychotic patients than among non-psychotics. This might favour its status as a "vegetative neurosis."

Bronchial asthma is not significantly less frequent among psychotics than non-psychotics. This emphasizes the importance of physical factors or of emotional factors at a psychotic level.

Diabetes mellitus is approximately as common among psychotic patients as in an unselected population. This either favors physical factors, or the hypothesis that the relevant emotional disorders are at a psychotic level.

Rheumatoid arthritis is rare among psychotics. This might support its designation as a "motor neurosis."

An elevated blood pressure is about as common among psychotic patients as among patients in general medical practice. This might favour the presence of physical in addition to emotional factors, since the high incidence renders psychotic factors less likely.

Hyperthyroidism is not common among psychotics, but no comparative incidence for non-psychotics is available.

With minor exceptions the sex ratios for these disorders are similar among psychotic and non-psychotic individuals.

J. C. Marfatia.

ANXIETY HCL SECRETION AND PEPTIC ULCER ETIOLOGY, Mahl. G. F.: Psychosom Med. 12: 158, 1950.

1. It is impossible to make a critical evaluation of an oral-dependency and an anxiety hypothesis of peptic ulcer etiology solely on the basis of available anamnestic or psychoanalytic studies of personality processes in peptic ulcer patients. A method which would enable one to do so is briefly described.

2. Both the oral-dependency and the anxiety hypothesis assume that increased HCL secretion is associated with the emotional processes emphasized. There are no published experimental data, positive or negative, concerning HCL secretion during the arousal of unconscious wishes to be loved, to eat, or to be fed. There is evidence that chronic overt anxiety behaviour in dogs and conscious chronic anxiety in humans are positively associated with increased HCL secretion. Some of the results are contradictory, however, and further studies, especially at the human level are needed. Such studies also aid in resolving the contradictory predictions of HCL secretion made by Cannon's emergency theory of emotions and by an anxiety hypothesis of peptic ulcer etiology.

3. A study of the gastric acidity of male students during the undergraduate examination period and during control periods is reported. The gastric acidity of these students was significantly higher during the examination period than during the control periods. The risk in gastric acidity was very closely related to the degree of conscious anxiety manifested by these subjects. These results agree with an anxiety hypothesis of peptic ulcer etiology; they do not bear directly upon an oral-dependency hypothesis.

4. A recent critique of an anxiety hypothesis of peptic ulcer etiology and of a previous experiment of the writer is considered. It is shown that this critique did not adequately describe the experimental procedure or the results of the study is discontinued. The theoretical objections raised in this critique are shown to be a function of confusion of the differential role of anxiety in the conversion neuroses and in the vegetative neuroses. The reluctance to consider the autonomic concomitants of anxiety is regarded as a joint result of the history of psychodynamic theory

and the unqualified extensions of Cannon's emergency theory of emotions of chronic emotional processes.

5. Possible fruitful lines of research for a comparative evaluation of the oral-dependency and anxiety hypothesis of peptic ulcer etiology are discussed.

J C. Marfatia.

ADAPTIVE REACTION TO STRESS, Selye, H. and Fortier, C.: Psychosom. Med. 12: 149, 1950,

1. Following a brief outline of the endocrine aspects of the General-Adaptation-Syndrome and of the so-called "Diseases of Adaptation", the participation of nervous mechanisms in these biologic reactions is considered.

2. Important alterations in the morphology and function of the nervous system can result from hypo-or hyperactivity of the pituitary-adrenal system, the main endocrine regulator of adaptive processes.

3. The coexistence of disordered endocrine mechanism with psychoneurotic or psychotic states, suggests some relationship between pituitary-adrenal activity and mental processes. The precise nature of this relationship is not yet established.

4. Alarming stimuli of a neurogenic or psychogenic nature are particularly potent activators of the pituitary adrenocorticotrophic function and produce rapid and intense alarm-reactions.

5. The corticotrophic effects of physical stress is apparently independent from any nervous mechanism; it is not prevented either by complete deafferentiation of the pituitary, or by the administration of autonomic blocking agents.

6. However, the possibility is considered that, unlike physical stressor agents, neurogenic stimuli may require a neurohumoral machanism to elicit the release of pituitary A.C.T.H.

7. Recent experiments indicate that many effects of mineralocorticoids are inhibited by simultaneous treatment with glucorticoids, yet on certain target organs the two types of hormones act synergistically. The importance of these interactions is stressed in connection with the concept of the diseases of adaptation.

J. C. Marfatia.

STRESS AND THE ADRENAL CORTEX with Special Reference to Potassium Metabolism, Hoagland H.: Psychosomatic Medicine, 12: 142, 1950

The fact that steroids modify both brain electrolytes and certain aspects of brain function is suggestive in relation to the author's finding of abnormal adrenal stress responses in schizophrenic patients. The author has seen that normal men, in contrast to most schizophrenic patients, fluctuate in rate of potassium excretion with modification of rates of release of their adrenal steroids in response to wide variety of stresses. The author has also seen that potassium is lost from the brain of rats in response to stress and that this loss may be prevented by certain steroids. It is tempting to consider that repeated failure of normal movement of tissue potassium accompanying a wide variety of stresses may play a cumulative role in the development of schizophrenic behaviour characterized by the establishment of conditioned responses involving inappropriate affect and disturbances of association, attention and consciousness. While there is no direct evidence for this hypothesis, and it may well be incorrect, the author presents it here as a target for criticism through further experimental tests.

J. C. Marfatia.

IMPAIRMENT OF ABSTRACT BEHAVIOUR FOLLOWING BILATERAL PREFRONTAL LOBOTOMY, Grassi; J. R.: Psychiatric Quarterly, 24: 74, 1950,

1. Thirty-two pre-frontal lobotomy patients were given a battery of psychological tests to investigate changes in intellectual function resulting from lobotomy.
2. The Wechsler-Bellevue Test revealed no significant reduction in general intelligence, or any evidence of impairment which could be attributed to the surgical procedure. Increased intellectual efficiency with increases in full scale. I. Q. of 1 to 21 points occurred in 28 out of 32 cases.
3. The Graphic Rorschach indicated a change in personality-structure and traits, corresponding generally with changes in the clinical picture. In a large number of cases, organic features were suggested by the Graphic Rorschach, later retesting indicating they were of a temporary nature.
4. The Grassi Block Substitution Test revealed marked impairment of abstract organization and inability to shift from a concrete to an abstract approach, suggestive of organic pathology resulting from the lobotomy. The impairment, however, disappeared almost entirely within the first year.
5. Prognostic criteria might be established on the basis of the performances on the Grassi Block Substitution Test and the Graphic Rorschach. The presence of decreased scores in block performances immediately following operation, with increased scores six months later, seemed to be significantly related to the degree of clinical improvement manifested. A shift to an extreme form of blot-dominance on the Graphic Rorschach as a result of the operation from a previously different level or performance may also prove to be a valuable prognostic criterion.
6. The results of the psychological measurements used do not contraindicate bilateral frontal lobotomy but rather support it as a therapeutic procedure.

J. C. Marfatia.

PERSONALITY CHANGES AFTER PRE-FRONTAL LEUCOTOMY: Petrie, A.: Brit. J. Med. Psychol 22: 200, 1949,

Instead of giving a detailed summary, an attempt will be made to outline the post-leucotomy patient's personality characteristics, in so far as these have been ascertained on the basis of objective tests. After nine months rather than three months does this outline more clearly support the hypothesis with which this paper opened.

Measures associated with neuroticism show a decrease; the patient is less suggestible, has smoother work surves, and has a changed attitude towards himself. The decrease in measures characterizing the anxious, depressive, introverted type is very marked. He is less persistent in a situation requiring endurance; he blames himself less and for fever characteristics; he lives less in the past and more in the present and future; he has lower motor perseveration scores; he goes more for speed and less for accuracy; he shows a greater appreciation of sex jokes in comparison with non-sex jokes. He has dropped in verbal intelligence scores, and shows a slight gain in performance scores.

On the intellectual side he shows a loss in verbal I. Q., a particular loss in comprehending social attitude unrelated to his immediate environment, and a loss in learning ability. He has gained on routine tasks but loses on tests where impulsiveness is penalized. He shows a less critical attitude in his use of language.

Nearly all these changes appeared after three months; the confirmation of their presence after nine months provides strong grounds for believing that with this particular operation, these are some of the changes which can be anticipated in this type of population.

The Connecticut Lobotomy Committee (1948) reported that if a change is to appear in a leucotomy patient it appears after 3 months. The authors have found this to be true about many traits, but there are exceptions. Some changes are clearly shown only after 9 months, some tendencies are accentuated and some are damped down. For example, motor perseveration and persistence involving endurance continue to decrease during the year after operation; speed and mistakes continue to increase. Increased distractability manifests itself clearly only after the longer period and reversed the earlier impression: Planning, as measured on the Mazes, appears to improve after the early loss, and so on.

There was a suggestion in the author's results of the relationship between some of the scores on the self-blame questionnaire (and the changes in the degree of self-blame and prognosis. This pointer will be followed up and the relationship ascertained between the personality pattern prior to leucotomy and the success of the operation. It is hoped also to ascertain, the relationship between the extent of the changes and the mental health of the patient after leucotomy.

Some of the changes reported here may be regarded as undesirable. Whether they are inevitably associated with the operation of leucotomy, in which a more anterior, less extensive or unilateral cut is made, remains to be shown. The investigations which have been described are now being carried out on patients who are undergoing rostral, unilateral and bilateral leucotomy at St. George's Hospital. The number of cases to date makes it impossible to give anything but highly tentative conclusions at this stage. There is, however, a distinct impression that some of the changes reported are less marked if the operation is less extensive.

J. C. Marfatia.

THE ASSOCIATION OF CERTAIN VEGETATIVE DISTURBANCES WITH PSYCHOSES: Ross, W.D. et al.: Psychosom. Med. 12: 170, 1950.

The occurence of various vegetative disorders in relation to psychiatric diagnosis within the population of a mental hospital in Canada has been examined and the relationship determined by statistical evaluation. No statistically significant association between a particular type of psychosis and bronchial asthma, diabetes mellitus, rheumatoid arthritis and hyperthyroidism could be demonstrated.

A statistically significant association was found between peptic ulcer and the manic type of manic depressive psychosis. This observation is considered in the light of the common hypothalamic mechanisms involved in the two conditions and with reference to the psychoanalytic feature of oral aggresiveness which has been described for both disorders.

Elevated blood pressure occurred most frequently in the older age group of patients and in those with involutional melancholia. It was significantly low in catatonic dementia praecox and absent among epileptic patients. Statistical analysis indicated a negative correlation of hypertension with epilepsy even when allowing for age. Contracts can be made between the personality characteristics which have been described for hypertensives with those present in catatonics and in epileptics.

J. C. Marfatia.

VENEREAL

CLINICAL EVALUATION OF A NEW PYROGENIC AGENT, Kierland, R.R. and Kulwin, M.H.: Arch: Derm & Syph. 62: 571-572, 1950.

Pyretotherapy is one of the recognised nonspecific treatments useful in many recalcitrant diseases of the skin. The authors tried a new pyrogenic agent, pyromen in 49 dermatologic patients. Pyromen is a non-protein purified product obtained from **Pseudomonas acruginosa.** It is administered intravenously, with 25 micrograms (0.5 cc.) as the initial dose, on alternate days. An oral temperature of 102°F is considered enough for the purpose and the subsequent dose is adjusted accordingly. Pyromen was used with the same success as typhoid vaccine in the following conditions: atopic dermatitis, neurodermatitis, psoriasis, seborrhoeic dermatitis, acne and congenital syphilis. It has been successfully used in the treatment of neurosyphilis, by Lousen and Liebert, who compared its action with that of malaria and typhoid vaccine. The authors conclude that but for a mild to moderately severe headache there are no serious side reactions as observed with typhoid vaccine, which is a distinct advantage.

T. K. Mehta.

PRIMARY CUTANEOUS NEISSERIA GONORRHOEAE INFECTIONS, Scott, M.J., and Thomsen, J.: Am. J. Syph., Gon. and Ven. Dis. 34: 262-264, 1950.

Medical literature hardly contains any record of primary gonococcal infection of the skin. The histologic structure of the skin is regarded as impenetrable to the gonococcus. In these circumstances, the authors consider it interesting to report three cases of gonococcal cutaneous penile infections.

All the three patients were white male soldiers of 21, 22 and 30 years of age. After an incubation period of about five to seven days following exposure, all of them suffered from a dorsal abscess of the skin of the shaft of the penis. The abscess was free from underlying structures. The smears, of the pus obtained on incision of the abscesses, were positive for gram negative intracellular diplococci morphologically consistent with **N. gonorrhoeae.** The cultures on chocolate blood-agar with brain-heart infusion base under low oxygen and under high carbon dioxide atmosphere were positive for **N. gonorrhoeae** as confirmed by fermentation and oxidase tests. There was bilateral, firm, discrete, non tender inguinal adenopathy in all three cases, but serologic tests for syphilis were negative in all the three. All cases responded to penicillin and sulphonamide (sulphathiazole) treatment.

There is nothing characteristic about primary cutaneous gonococcal abscesses. Therefore, in conclusion, the authors recommend routine smears and cultures in cutaneous abscess located in genital region. Only thus can cutaneous gonorrhoeal infection be unmasked.

T. K. Mehta.

DONOVANOSIS, Marmell; M.: Am. J. Syph. Gon. & Ven. Dis. 34: 88-92, 1950.

After giving an exhaustive review of varied nomenclature for the fifth venereal disease or granuloma inguinale and proposing one more viz., 'Donovanosis,' the author gives, pertinent and thorough details regarding its laboratory diagnosis.

Donovanosis is a specific infection and its diagnosis depends on the demonstration of the etiological agent in the tissues involved by the lesions. Since the organism, **Donovania granulomatis,** presents unique morphological and tinotorial characteristics, the tissue smear offers a simple and reliable means of diagnosis, provided the smear is properly taken, well stained and carefully examined. After taking a smear for Gram's stain and a specimen for dark field examination, the lesion is scraped to obtain subsurface tissue for a smear for donovan bodies. This is best obtained from the granulation tissue or from the margin of the lesion. In healed lesions the specimen may be obtained with a biopsy punch and a smear made with the cut surface and a section from the remaining part. In the author's hands smears gave better and more constant results than sections. The tissue from the scraping or biopsy is placed upon a glass slide and a smear obtained by spreading the material with another slide. The smear is then stained with Wright's stain. The stained smear is then examined under the microscope for encapsulated coccoid, diplococcoid or bacillary bodies—the donovan bodies—present within large mononuclear cells. The organisms stain variously from blue to deep purple surrounded by a clear or faintly stained pink capsule. The picture is characteristic and when once seen is not forgotten. The above description of the donovan body is diagnostic. Atypical forms have been described.

T. K. Mehta.

NOTICE TO CONTRIBUTORS

THE INDIAN JOURNAL OF MEDICAL SCIENCES which appears monthly, publishes original articles in all branches of medicine and allied sciences, case reports, progress reviews, book reviews, summary of current medical literature and author's summaries. Papers submitted for publication and all editorial communications should be addressed to the Editor, Indian Journal of Medical Sciences, Back Bay View. New Queen's Road, Bombay 4.

Papers submitted for the JOURNAL are accepted on the understanding that they have not been and will not be published in whole or in part in any other journal; they are subject to editorial revision.

MANUSCRIPTS should be in double-spaced typing on one side on quarto or foolscap sheets, with a margin of not less than 2 inches. They should bear the name and full address of the author to whom proofs are to be sent. A paper should conclude with a brief summary giving in numbered paragraphs the results and conclusions described in the paper; it should not exceed 1/20th of the length of the paper.

TABLES.—Tables should be typed on separate numbered sheets and referred to the text by Arabic numerals.

ILLUSTRATIONS.—Illustrations will not be accepted unless they reach a certain standard of excellence technically, present an attractive appearance and add significantly to the value of the presentation. They are to be referred to in the text by Roman numerals. Legends or captions are to be typed on separate sheets and numbered correspondingly. Line drawings and graphs, which should be about twice their intended final size, are to be carefully drawn in Indian ink on tracing linen, or card board, or stout smooth white paper; blue-lined graph paper of good quality may be used for graphs. Lettering of drawings and graphs must be lightly written in pencil. When half-tone reproduction of X-ray or other illustrations is required the author is advised to send the original film unless he wishes to bring out special points in a print of his own choice. Photographs and photo-micrographs should be printed on glossy paper, should be larger than the size desired for reproduction, and if transmitted through the post in a tube, should be rolled with the picture outside.

REFERENCES.—At the end of the paper references should be arranged in the alphabetical order of the author's names and should include: author's name, followed by initials; the name of the article, name of journal, volume underlined; pages, and the year. References made to books should include the author's name followed by the title underlined, pages, town of origin, the publisher and the year.

Examples. 1. Coller, F. A., and Maddock, W. G.; The Function of Peripheral Vasoconstriction, Ann., Surg. **100** : 983-992, 1934.

2. White, J. C., and Smithwick, R. H.: The Autonomic Nervous System, pp. 271, New York, the Macmillian Company, 1941.

Citations in the text should be by the author's name followed by the number listed in the reference.

PROOFS.—Contributors will receive one proof in galley, but it will be assumed that all but verbal corrections have been made in the original manuscript.

REPRINTS.—25 reprints of an article will be given to the author or divide among the authors. Additional reprints can be supplied at cost price if application is made when the proofs are returned.

COPYRIGHT.—Papers which have been published become the property of the Journal and permission to republish must be obtained from the Editor.

Indian Journal of Medical Sciences
(INCORPORATING THE MEDICAL BULLETIN)

VOLUME 5 JUNE 1951 NUMBER 6

COPYRIGHT BY THE INDIAN JOURNAL OF MEDICAL SCIENCES

THE ACTION OF PROCAINE

SOME OBSERVATIONS ON ANIMALS, OF CLINICAL VALUE

V. Ishwariah, T. R. Krishnamurthy and Sarada Subramanyam *

The trend in therapeutics during the past decade or more is not only to find new therapeutic agents, but also to unearth new actions of the old drugs. The main or outstanding actions of some of the recognised drugs, often obscured the detailed study of their other actions. This may be seen in the following examples: (1) though the alkaloids of cinchona have been in use as antimalarials from 1640, their action and use in heart conditions is comparatively recent; (2) anti-histaminics today seem to break asunder the chains of allergy for which they were originally synthesised and are used in a variety of ailments; (3) urethane, that was associated with only hypnotic properties, is finding a new chemotherapeutic field in malignancy; (4) suprarenal cortical hormones once associated with mineral metabolism, today show new and baffling properties. On the other hand as pointed out by Burn[1] (1950)"......many substances used for quite different purposes in medicine, hitherto thought to have quite dissimilar modes of action, have many common properties." In line with these, the synthetic local anæsthetics of the procaine group have a wide range of action outside the sensory nerve depressent effect.

Procaine—its other properties: One of the striking properties of procaine or novocaine was observed when it was used in a 0.1 per cent saline solution, intravenously in cases of shock. Procaine tended to accelerate the flow of saline into the vein; a new 'venodilator' property was thereby brought to light. Further study of the compound suggested a wide field of therapeutic application, and is advocated today for conditions ranging from allergy to angina pectoris, pruritis to parturition. Procaine seems to evince (1) a curare-like (2) an atropine-like (3) a quinidine-like (4) a sympathomimetic (5) an antihistaminic and perhaps other actions. There is also some evidence of an ecbolic action. An aggregate of these effects may seem confusing and often unpredictable, when it is seen that it can exert simultaneously an analgesic, a sympathomimetic cum lytic and vasodilator action. To a less extent, procaine is also said to exert a parasympathomimetic cum lytic and histamine-like actions.

---

* From the Department of Pharmacology, Stanley Medical College, Madras.

Aims of the study: We were impelled to undertake this study amongst other reasons, to dispel the fear among many clinicians, of the intravenous use of procaine. Unforeseen catastrophic results when procaine was used subcutaneously or intrathecally have been noticed by some, which is said to be due to access of the compound to a vein, by which route it was deemed extremely toxic. The fear had deterred its use in therapeutics. The study was therefore mainly an attempt to establish the safety of its intravenous administration. Data were also to be made available as to maximum dose tolerated, in animals, the effect on different animals, the effects of rapid and slow administration in varying strengths, and lastly its pharmacological actions on circulation and respiration.

Materials used: Dogs weighing 6—9 Kg., cats 2—3 Kg. and rabbits of 1.5–2 Kg. were used in this study. As dogs were more easily available than cats or rabbits, repetition of the experiments were carried out either on cats or rabbits; two dogs roughly being used for one of either of the two others. Procaine or para-amino benzoyl diethylamino ethanol was used in the form of the hydrochloride, which is readily soluble in water and normal saline, and is incompatible with alkalies, oxidising and reducing agents.

I. Effect of procaine on unanæsthetised animals: The marginal ear vein in rabbits and any accessible one in dogs and cats were selected for procaine administration. In one series of animals (four dogs) 5 c c. of a 1 per cent solution was administered in about one minute. As no perceptible effect was detected after an hour, 6 c c. of the same strength was repeated again in about a minute. With still no perceptible effect, the dosage after an hour was raised to 7 cc., administered in the same time. All the animals received 10 c.c. or an aggregate of about 400-450 mg. spread over five to six hours. Similarly cats weighing 2 and 2.7 Kg., received 1, 2, 3 and 4 c.c. at intervals of an hour with the precautions. The animals were watched for a period of 2-3 weeks for any delayed toxic effects. No appreciable toxic effects were noticed. Rabbits stood a proportionate dosage. (In cats gentle whiffs of chloroform had to be given sometimes to facilitate injection.)

In another series of two dogs weighing from 7–8 Kg. procaine was administered in 1 per cent strength, but very rapidly (10 sec.). Here again 7–8 c.c. of the solution showed no immediate visible effect on the animals. Emboldened by the 'non toxic' effect of 1 per cent strengths in quantities up to 8 c.c., the strength of the solution was raised to 3 per cent or 30 mg. per cc.

It is axiomatic that a large dose of any drug can be given slowly with safety (barbiturates and other anæsthetics) while a smaller dose if given rapidly can cause trouble. We now administered 5 cc. of the 3 per cent in about 1.5 minutes. Noticing no visible effect, another animal was selected where 10 c.c. of a 3 per cent solution (300 mg.) was administered in 5 minutes. The dog now reeled, felt 'giddy,' showed signs of incoordination, retched violently and began gasping. After about 20 minutes it revived, responded to calls and showed inclination for food. Having verified the effects with this dose on other animals, we reduced the dose to 8 cc. of a 3 per cent solution with no visible change in the animal. We thereby fixed the tolerated or 'toxic dose' between 9—10 c.c. of a 3 per cent solution *i.e.*, 250—300 mg. These animals were also under observation for 15—20 days after the injection. After 3 weeks these animals were injected with 50, 100, 200 and 300 mg. of novocaine in 3 per cent strengths on consecutive days to see if the earlier injections had acted as sensitising or desensitising agents. There was no apparent indication of either. Graubard[4] (1947) found that in rabbits there was a possibility of cumulation, as procaine was more slowly detoxicated. This is possible if the injections are repeated hourly.

II. Effects of procaine on circulation and respiration: Observations were next made on the effects of procaine on the carotid blood pressure and respiratory movements. Dogs weighing 7-9 Kg. and cats of 2-3 Kg. weight were given paraldehyde 2.5 c.c. per Kg. by means of a stomach tube. The carotid blood pressure and intra-tracheal pressure were recorded as usual on a kimograph. Procaine solutions in 1 per cent strengths were used. Artificial respiration was ready for emergencies. A start was made with 1 c.c. of a 1 per cent solution injected into the saphenous vein and washed in with about 2 c.c. of saline. The dose was gradually raised to 2, 3 and 4 c.c. *i.e.*, 20 mg., 30 mg., and 40 mg., at intervals. There was in every instance a fall in blood pressure, approximately in proportion to the dose The blood pressure however returned to normal within a short period. (Fig. 1). shows the effect of varying doses on blood pressure and respiration.

When a dose of 60 mg. or 6 cc. of a 1 per cent solution was injected in dogs, the fall in blood pressure tended to be more prolonged. Respiratory embarassment made its appearance. The blood pressure even here tended to return to normal, quicker with artificial respiration. Respiration tended to remain depressed for a longer period, but once circulatory depression was marked, artificial respiration was of no avail. From these observations we concluded that the depressent effect of procaine on respiration was more marked and lasting as against its effects on circulation. With a dose of 60 mg. or 6 cc. of a 1 per cent solution, fall in blood pressure was more lasting and respiration failed. Artificial respiration at this stage raised the blood pressure to satisfactory heights which remained stationary for a while. With 80 mg. the fall was permanent and artificial respiration was of no avail. (Fig. 2).

Higher strengths *i.e.*, 2 and 3 per cent procaine solution revealed that the effect on circulation and respiration depended mainly on the aggregate dose. It is to be noted here that 250-300 mg. (9-10 c.c. of a 3 per cent strength) in an un-anæsthetised animal showed signs and symptoms comparable to 80 mg. (8 c.c. of 1 per cent solution) in animals of similar weight under paraldehyde, chloralose or urethane anæsthesia. This observation again warrants the conclusion that in an animal already depressed by an anæsthetic, the respiratory centre is more easily upset. After complete atropinisation, 50 to 80 mg. of procaine produced a similar fall in blood pressure, whereby indicating that vagal inhibition was not the cause of the fall in blood pressure. After very large doses 400—500 mg. in one dose for a dog weighing 7 Kg. autopsy revealed a dilated and flabby myocardium, suggesting the possibility of cardiac damage. The momentary fall in blood pressure after small doses is due to vasodilation mainly. The particular vessels taking part in this dilation, (surface; interior, or other factors) is the subject of further study by one of us.

III. Anæsthetic and procaine effects. With an idea of the aggregate amounts that an unanæsthetised animal and one under paraldehyde anæsthesia could stand, we studied the effect of procaine on animals under different anæsthetic agents. Chloralose 0.11 Gm. per Kg. was administered intramuscularly to dogs to induce complete anæsthesia Procaine in 1 per cent strength was administered in varying doses as in the previous case with paraldehyde anæsthesia. A similar fall in blood pressure and respiratory effects were noticed when either 5 c.c. of a 1 per cent solution or 2.5 c.c of a 2 per cent solution was used. The effects, however were a little more marked, particularly the effect on respiration which was possibly because this anæsthetic is a greater depressent of the vital centres than paraldehyde (Fig. 3).

Otherwise the pattern of effect was similar to the previous one. Cats under urethane anæsthesia *i.e.*, 1.8 Gm. per Kg. intramuscularly, also showed similar effects.

In the next series of observations, kemithal or sodium 5 cyclohexenyl 5 allyl 2 thiobarbiturate was used as the anæsthetic, *i.e.*, 300 mg. intravenously. The animals were administered with 40 mg. per Kg. intravenously to produce complete anæsthesia. Blood pressure and respiration were recorded as usual. The injections however had to be given at shorter intervals as the anæsthesia was not of the same duration as the previous ones. When a dose of 100 mg. or 10 c.c. of a 1 per cent solution of procaine was administered, there was no appreciable effect on circulation and respiration. The dose was doubled to 200 mg. (10 cc.

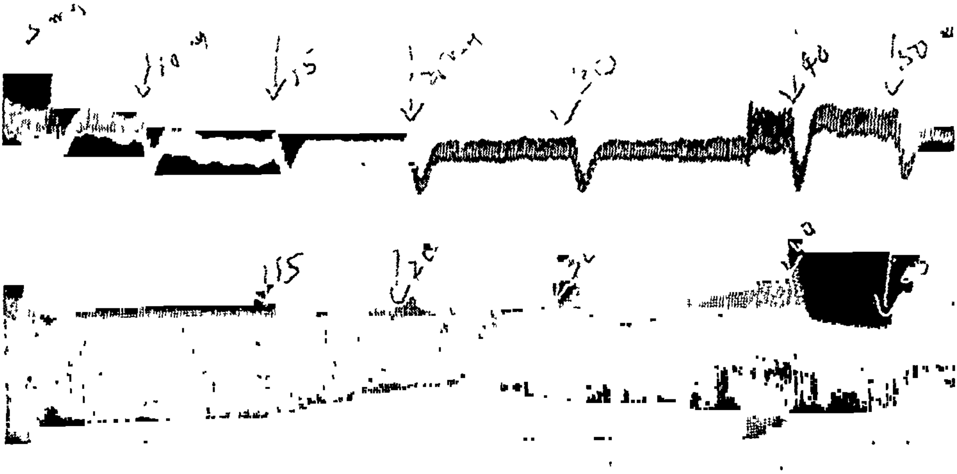


Fig. 1. Effect of increasing dose of Procaine on Blood pressure (upper) and respiration.

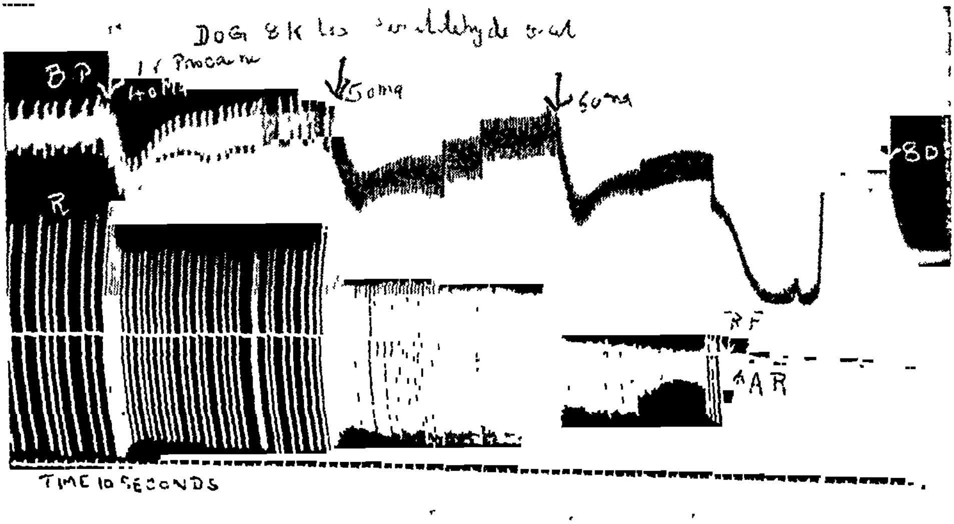


Fig. 2. Effect of 60 and 80 mg. of Procaine on Blood pressure (upper) and respiration.

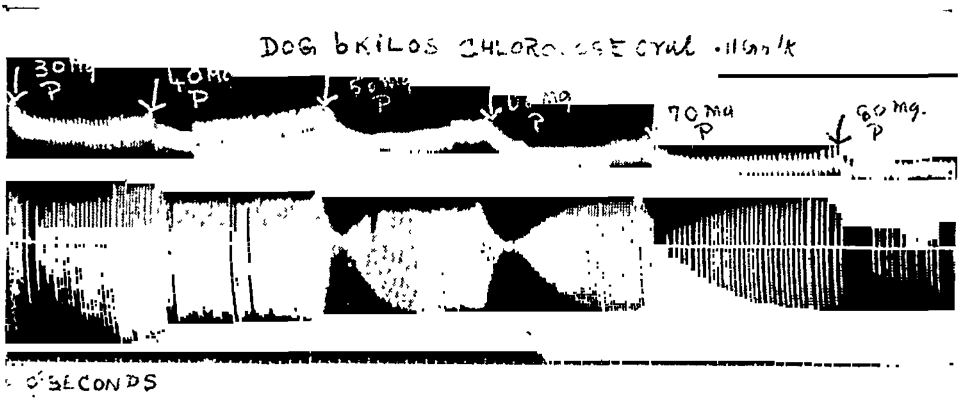


Fig. 3. Effect of Procaine on Blood pressure (upper) and respiration on a dog under chloralose. The depressant effect is a little more marked.

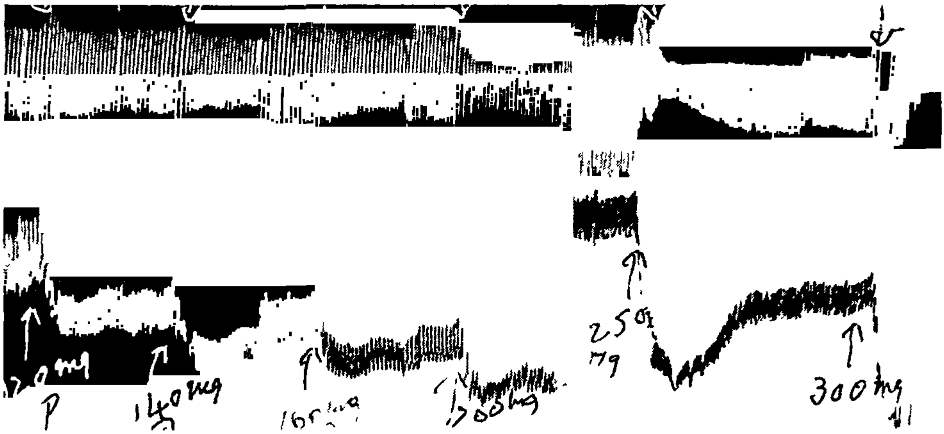


Fig. 4. Effect of Procaine on Blood pressure (lower) and respiration on a dog under kemithal. Larger doses are tolerated.

of a 2 per cent solution) when a slight fall in blood pressure and respiratory embarrassment were noticed. The effect however passed off. After some time, the same animal was administered with 300 mg. or 10 c.c. of a 3 per cent solution. The blood pressure now dropped appreciably (Fig. 4). Respiration ceased for a minute when artificial respiration had to be utilised, which helped to revive circulation for sometime, but when artificial respiration was stopped the circulation again tended to fail. Continued artificial respiration failed to revive the animal. The animals in this series received about 600 mg. in about an hour and three quarters. These observations revealed that animals under kemithal anæsthesia—possibly any barbiturate—stood much higher doses, sometimes up to four and five times that under other anæsthetics.

IV. Procaine in fibrillation of the heart. Anæsthetists like Burstein[2] (1949) had observed the restorative effect of procaine in cases of heart failure under cyclopropane anæsthesia. We attempted to induce fibrillation in animals under chloralose anæsthesia by administering adrenalin intravenously during forced respiration of chloroform. There was a sudden drop in blood pressure and the animal rarely revived. It was assumed that the failure of circulation was due to fibrillation of cardiac muscle. Inhalation of plain chloroform caused only a small fall in blood pressure. Acute myocardial poisoning enough to cause heart failure after chloroform was not found at autopsy. Administration of 5-10 c.c. of 1 per cent procaine to animals showing circulatory failure as a result of adrenalin and chloroform did not revive heart function. A case is reported by Roualle, [10] (1950) of complete cardiac arrest in which systole persisted for 45 minutes despite intracardiac adrenalin and cardiac massage, but revived with intra-cardiac procaine and continued to function for 4 hours.

V. Procaine as vasolidator—clinical observation. The following clinical conditions were treated with intravenous procaine (1 in 1000 solution) administered at the rate of 10-20 c.c. per minute, where an aggregate of 100 c.c. was found necessary: (1) embolism (2) vaso-spastic conditions and thrombo angitis obliterans (3) arterio-sclerotic gangrene (4) migraine (5) angina pectoris (6) acute exacerbations of primary hypertension and (7) periarteritis nodosa. When about half the amount had been injected, the patient felt considerable relief from pain, sometimes a feeling of pulsation was noticed in the region. The affected part felt warm, 2½°—4°F above the original temperature. The effect usually lasted 4-6 hours and invariably required a second injection of a similar amount after 24 hours. After 4—6 such injections (one daily) results tended to be more lasting and in many cases obviated the necessity for an amputation. (Permitted to extract, by Dr. V. Rajagopalan, Anæsthetist, General Hospital, Madras, who is publishing details separately.)

DISCUSSION.

Only recently have the many-sided actions of procaine found therapeutic application. The simplicity of administration is contributing to its popularity, though some clinicians are much too alive to its toxic propensities. Three possible toxic manifestations may be expected. A profound vasomotor depression is occasionally encountered in the first instance clinically. A second possible untoward action is excitement and convulsions which may go on to medullary paralysis, mainly respiratory failure. Our findings corroborate the earlier observations that large doses cause respiratory failure; in some cases, animals could be kept alive with artificial respiration, as circulation tended to continue undamaged though Taylor *et al* (1950) noticed respiratory and cardiac arrest at the same time. A third possible manifestation is allergy. As the anti-allergic drugs can themselves be allergic, so can procaine, which is also an anti-allergic compound. Cardiac standstill after fibrillation is rare after procaine though this was thought to be the case when occasional catastrophes resulted when procaine was used subcutaneously for infiltration anæsthesia. The reason according to some is that the admixed adrenalin entering circulation, tended to cause ventricular fibrillation. Others hold the view that procaine stimulated the output of adrenalin which caused ventricular fibrillation. Corroboration of either view by factual data is lacking. It must however be said that the rapidity of administration of any substance by the intravenous route increases risks, though in our series of animals, not much difference was noticed when 10 seconds or 1½ minutes were taken to inject 10-50 mg. into a vein. Animals can stand several times the toxic dose by the intra-hepatic route. Clinically, when procaine is administered intravenously to a patient to allay pain, any increased excitement, restlessness, garrulity or twitching of muscles, is an indication for stopping or slowing the administration. Dyspnœa is a more serious sign of toxic manifestation.

The present study with varying dosage on different animals *i.e.* cats, dogs and rabbits revealed that procaine up to 15 mg. per Kg. in 1 per cent strength when administered slowly, is a safe therapeutic procedure. Clinically this dosage and strength have been deemed high. Not merely are there risks associated with this dose and strength, but smaller doses and weaker strengths produced the desired effect according to some. Lancet[3] (1950) advocated 4 c.c. of 1 per cent solution given intravenously slowly or 0.1 per cent in saline up to 500 c.c. in half an hour for a case of status asthmaticus. Both measures yielded satisfactory results. MacLachlin[8] (1949) noticed idiosyncrasy with procaine, giving rise to symptoms of either (1) nervous convulsions which is easily controlled by intravenous barbiturates or (2) a respiratory syndrome of the asthmatic type relieved by 2 minims of 1 in 1000 adrenalin subcutaneously. Occasionally, a 1 per cent strength of procaine produced a preconvulsive tetany if anæsthesia was light. Large doses of procaine sometimes tended to nullify the depressive effect of anæsthesia.

The integrity of the liver seems to determine one or other of the toxic manifestations of procaine. Procaine itself in optimum doses does not damage the liver. Steinberg,[12] (1949) studied liver function as determined by the cephalin flocculation test, up to 10 c.c. of a 1 per cent solution. There was no evidence of impaired liver function in man. Our observations on animals for two and three weeks after large doses of procaine did not indicate any evidence of liver damage or damage to any other vital organ. It has also been observed that the administration of ascorbic acid as a prelude to procaine administration will lessen the toxic action. Possibly ascorbic acid prevents percolation of procaine through the capillary wall. This is not inconsistent with the use of procaine in cases of joint, muscular and other pains, where procaine is said to accumulate in inflamed areas due to the increased capillary permeability.

Procaine has also been administered orally. Roke and Lajtha[9] (1950) administered 100 c.c. of 1 per cent procaine by mouth, taking about five minutes to administer the amount. Complete paralysis of the pyloric sphincter was noticed in 10 minutes, while the stomach movements remained unchanged. Reflex closure of the pylorus normally produced by mechanical irritation, was also abolished. In cases of chronic gastric ulcer, vomiting was greatly relieved. In some cases of carcinoma of the stomach, oral procaine enabled the patient to be fed normally which otherwise was not possible on account of the vomiting that was associated. The patient was made fit for operation. On the basis of these findings and after administration of atropine and adrenalin a view was postulated that physiological control of the pyloric sphincter 'rests with the local nervous system and that this system can be paralysed by procaine given orally.'

Procaine and heart function: Circulatory depression seems to be the most severe hazard in procaine therapy for the reason that it gives no warning of the impending fall of blood pressure. If the circulation is watched closely, gradual increasing doses could be attempted. Otherwise, about 5 c.c. of a 1 per cent solution per minute is the path of safety. Some prefer to give 0.1 per cent strength but 50-100 c.c. where the aggregate amount is the same. Our findings suggest that aggregate amounts at a time counts more than the strength of the solution used. The more the concentration the more slowly is it to be administered. As mentioned before the exact reason for the circulatory hazard is still in doubt. The presence of adrenalin in the official or other procaine-adrenalin compounds, has been incriminated. Procaine is also said to 'provoke' the suprarenal to secrete more adrenalin. There is a third view that one of the disintegration products of procaine acts like adrenalin. Procaine on hydrolysis in the blood releases para amino benzoic acid and diethyl amino ethanol. (Diethyl amino ethanol is sometimes used as a solvent for some substances of low solubility). The action of diethyl amino ethanol (DEAE) has been studied by Russer and Hergot[11] (1950) on isolated heart animals. DEAE is also a constituent of antispasmodics like trasentin and parpanit. In varying concentrations, DEAE either augments or inhibits the contractile action of the frog's heart. Higher concentrations reinforce while lower concentrations inhibit this action. Similarly the inhibitory action of acetyl choline is augmented by low concentrations and inhibited by higher concentrations of DEAE. The inhibitory action of DEAE may possibily explain the claim of some anæsthetists that procaine corrects fibrillation of the heart under cyclopropane anæsthesia.

In a private communication to the senior author (V. I.) the anæsthetists of the Madras Government General Hospital, Dr. Gowranga Rao and Dr. Rajagopalan said that cardiac irregularity and irritability under cyclopropane anæsthesia is corrected by 10-20 c.c. of a ½—1 per cent solution of procaine administered intravenously. In those cases where the circulation is feeble, they prefer larger amounts of procaine *i.e.*, 100 c.c. but in weaker strength *i.e.*, 0.1 per cent. Control observations with plain saline in 100 cc. doses failed to correct the heart, where the volume of the fluid introduced was not of any consequence. They had also used procaine in 1 per cent strength as a prophylaxis against the possibility of fibrillation. In our study on animals, fibrillation caused by chloroform and adrenalin were not corrected by novocaine. One may be inclined to run to the conclusion that the beneficient or adverse effects of procaine are mainly due to its disintegration product DEAE. Kraat *et al*[6] (1950) had compared the effects of procaine and DEAE on varying organs like the isolated heart, uterus, intestine, excised vessels etc., in mammals and found that a parallel between procaine and DEAE existed in the stimulation of the excised uterus and in the dilatation of mammalian vessels. In most other respects, procaine differs from DEAE. Quantitatively, on the excised uterus, procaine was 20-40 times as strong as DEAE. Hence the doubt still remains that all the effects of procaine administered intravenously are due to its disintegration product DEAE.

SUMMARY.

1. Procaine administered intravenously to unæsthetised dogs, cats and rabbits showed that animals tolerate 10—20 mg. per Kg. without any deleterious effect.
2. Animals anæsthetised with paraldehyde, urethane and chloralose showed a momentary fall in blood pressure up to 10 mg.

per Kg. In higher doses, circulatory and respiratory depression were more marked. Artificial respiration in most cases restored normal circulation.

3. Animals under kemithal anæsthesia stood 3-5 times the dose compared to other anæsthetic agents before circulatory or respiratory depression set in.
4. The concentration of the solution did not appreciably affect the result as much as the aggregate amount at a time, provided 2-3 minutes are taken to give 5-10 c.c. of a 1 per cent solution.
5. Procaine did not correct fibrillation of the heart induced by chloroform and adrenalin.
6. Clinically the vasodilator effect of procaine is salutory, preventing possible amputation in some cases.
7. The delayed or cumulative toxic action was inappreciable in a healthy individual with normal liver function, after large doses of procaine.

BIBLIOGRAPHY.

1. Burn, J. J.· Pharmacological Actions of Antihistamine Compounds, B. M. J. **2**: 691-693, 1950
2. Burstein, C L.: The Utility of Intravenous Procaine in the Anaesthetic Management of Cardiac Disturbances, Anaesthesiology **10**: 133-144, 1949.
3. Lancet, Editorial, Intravenous Procaine Therapy in Status Asthmaticus, 619, 1950.
4. Graubard, D. J. *et al.*: Micro Determination of Blood Levels of Procaine Hydrochloride after Intravenous Injection, Anaesthesiology **8**: 236-240, 1947.
5. Horan, J. S.: Intravenous Administration of Tetracaine, Arch. Int. Med. **85**: 972-979, 1950.
6. Kraat, C. P., Gruber, C. and List, A. G.: Observations on Diethyl Amino Ethanol, J. Pharm. and Exp. Ther. **98**: 111-119, 1950.
7. Long, J. H., *et. al*, The Effect of Intravenous Procaine on the Heart, Anaesthesiology **10**: 406-415, 1949.
8. McLachlan, J. A.: Intravenous Procaine—its Effect on the Liver Function in Man, Anaesthesiology **10**: 739, 1949.
9. Roka, G. M. D. and Laitha, L. G: Abolition of Pyloric Spasm by Oral Administration of Procaine Solutions, B. M. J. **1**: 1174, 1950.
10. Roualle, H. L. M.: A Case of Cardiac Arrest Relieved by Procaine, B. M. J. **2**: 712-713, 1950.
11. Russer and Hergot: Diethyl Aminoethanol on Isolated Smooth Muscle, Arch. Exp. Path and Pharm. **209**: 95, 1950.
12. Steinberg, B. L. : Intravenous Procaine—its Effects on Liver Function in Man as Determined by Cephaline Flocculation Test, Anaesthesiology **6**: 739-742, 1949.

SUITABILITY OF THE INDIAN MALE-TOAD BUFO MELANOSTICTUS IN DETECTING CHORIONIC GONADOTROPIN

S. M. Nadkarni *, and Miss R. S. Broker *

The Indian male-toad *Bufo melanostictus* is a very suitable and readily available animal in the diagnosis of pregnancy and some other conditions where chorionic gonadotropin is excreted in the human urine. In fact this species is more suitable than the more commonly found frog *Rana tigrina* inasmuch as unlike the latter, the toad shows no seasonal variation in responding to the pregnancy hormone. Moreover, the thyroxine pre-treatment found to be advantageous by Bach and Szmuk[2] (1949) was not observed to be of any particular advantage with *Rana tigrina.*

The toad thrives on live insect food and earthworms, both of which are rather difficult to obtain throughout the year. It is suggested that if the toads are kept in a cool place the metabolic processes are slowed down and the need for food is lessened [3, 12] Partial submersion of the toad in water results in the death of the animal; hence much water has always to be avoided. To keep the toad in the laboratory under as natural conditions as possible the animals may be isolated in numbered compartments in tin boxes measuring 1 ft. × 1 ft. × 8 ins. Gravel with water just sufficient to maintain the required moisture, is spread in the box. Each box is divided into four compartments, and its lid is perforated to effect adequate ventilation. The animals can be re-used eight days after a positive reaction and two days after a negative one has been obtained. When, however, the rest periods were shortened no false reactions were known to occur.

It is easy to distinguish a male from a female toad during the monsoon by the orange-red colouration of the skin covering the submandibular region in the male. It is, however, advisable to test all animals for spermatogenesis by injecting urine from a normal pregnancy case in a dose described below. Animals thus tested were used one week after the 'standardisation'.

METHOD.

The specimen of urine to be tested should be kept in a cool dark place before use. In order to avoid mortality among the animals due to injection of neat urine [2, 9, 10], its concentrates were used for injection into the dorsal lymph sac of the toad, although Haskins and Sherman[8] have preferred the intraperitoneal route. One disadvantage of using neat urine is that in the case of specimens of low specific gravity, large quantities of the specimen may have to be injected so as to avoid a false negative reaction. Such large doses of neat urine cannot be injected in the *B. melanostictus* because of its small size.

---

* Dr. K. T. Gajjar's Pathological Laboratory, Bombay 1.

The quantity of urine to be used for extraction was found to be 10 c.c. for the diagnosis of pregnancy. Experiments were carried out by using the concentrates from 10 c.c. and 40 c.c. of the same urines with specific gravity lower than 1010. It was observed that both doses gave positive reactions though the larger dose gave, as may be expected, a strongly positive one. Neat urine is used for the diagnosis of hydatidiform mole. Concluding from the observations made so far on such cases, it was found that 1/64 of a c.c. of neat urine was the dose diagnostic of this condition if it resulted in a positive reaction. Further observations are still to be made on more of these cases.

The two available methods for quickly concentrating urine specimens are Weisman and Coates'[15] method of precipitating the hormone with acetone, and Scott's[13] method of hormone adsorption with kaolin. As the former method was found more suitable, it was adopted. Experiments performed on both methods show that during the process of concentration more hormone is left unrecovered by Scott's method than by Weisman's method; although it is the observation of Dittebrandt[5] (1949) that "Using the acetone method an accuracy of 97.8 per cent has been got whereas by the kaolin adsorption method, 98.8 per cent accuracy is claimed."

Making use of the principle on which Weisman's method is based 20 c.c. of acetone are added to 10 c.c. of urine and the precipitate is allowed to settle. The supernatent fluid is saved for re-distillation to recover the acetone and the lower portion containing the precipitate is centrifuged. The precipitate is dried free from acetone by means of a suction pump (or by blowing air) and suspended in 1 to 2 c.c. of distilled water. It was not found necessary, for our purpose, to adjust the pH of the eluate to 5.5, as advocated by Weisman *et al.*[15] (1944). The clear supernatant fluid obtained after centrifuging the aequeous suspension is used for injection.

For injecting, the animal is held as shown in the plate. The needle is introduced into the skin covering the thigh dorsally and pushed very slightly deep and then forward just under the skin till the dorsal lymph sac is reached (central line of the lower one-third of the dorsum). The fluid is injected very slowly and the needle withdrawn several seconds after the material has been injected.[6]

The cloacal contents of the injected toad are examined microscopically at either half or one hour intervals. It is imperative to observe the animal for at least four hours after injection before a negative reaction is reported and it is equally important to examine the cloacal contents before injecting an animal, thereby excluding the possibility of a false

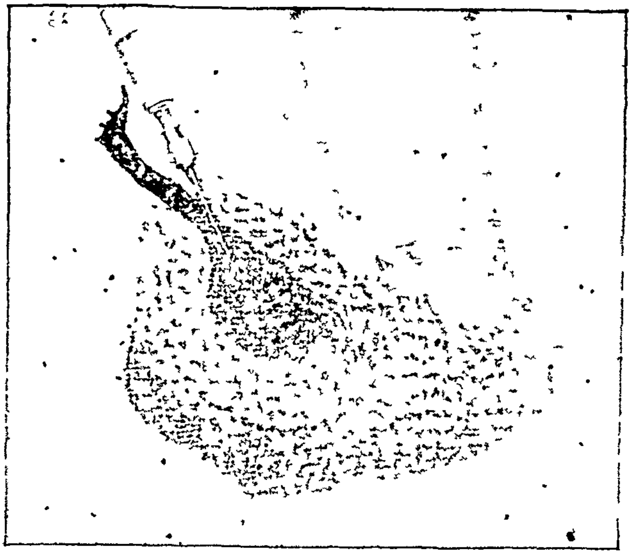


Plate showing how animal is held when injecting.

reaction. The presence of sperms in the cloacal contents of an injected toad is indicative of a positive reaction, irrespective of the motility or otherwise of the sperms.

OBSERVATIONS ON THE REACTION

Klopper and Frank[9] (1949) have observed when working with *B. vulgaris* that no spontaneous spermatogenesis occurs in the absence of female toads. This difficulty has not been encountered with *B. melanostictus*. It was found necessary to observe the test animal for at least four hours before a negative test was reported, as was concluded from the following evidence.

TABLE I. *The Reaction of B. melanostictus to chorionic gonadotropin.*

No. of animals injected.	Reaction given at							
	½ hr.	1 hr.	1½ hrs	2 hrs.	2½ hrs.	3 hrs.	3½ hrs.	4 hrs.
24	+							
87		+						
17		—		+				
1		—		—	+			
1		—		—		+		
1		—		—		—		+

+ = Positive. — = Negative.

D'Arcy and Gronwall[4] (1949) opined that the factors, (1) re-use of animals, (2) temperature and light conditions under which the animal is kept after the injection and (3) immaturity of the animal may be responsible for delayed reactions, but these were excluded as being causes of such reactions in the *B. melanostictus*.

FALSE REACTIONS

Haines[7] (1948) and Aznar-Ferreres[1] (1949) recommended that the cloacal sample of an injected animal should be examined three hours after an injection, for, according to them, a reaction positive at two hours cannot become negative at three hours. It is possible that the animal may eject its cloacal contents before three hours, and the third hour specimen may give a false negative reaction. The following is the observation with our experimental animals.

TABLE 2.—*Reactions at Varying Intervals.*

Animal Number.	Interval (in hours) at which the animal was examined after the injection									
	½	1	1½	2	2½	3	3½	4	5	6
13	+	+	+	+	+	—	—	—		
17	+	+	+	+	+	+	+	—		
5		+		+		—		+		
9		+		+		+		—		
4		+		—		—				
33		+		+		—				
76		+		+		+		+	+	—

+ =positive reactions; — =negative reactions.

From the above, it may be concluded that it is very important to examine the toad for sperms at one hour interval after an injection.

COMPARISON WITH STANDARD METHODS

The practicability of the various tests evolved for pregnancy diagnosis is rendered apparent by the following Table[14]:—

TABLE 3.—*Comparison of Different Methods.*

	Xenopus	A-Z (mice)	Kelso (rats)	Friedman (rabbits)	B. melanostictus.
Rapidity	4-18 hrs.	96 hrs.	24-30 hrs.	36-48 hrs.	1-4 hrs.
Simplicity	No operation.	Animal killed.	Animal killed.	Operation required.	No operation
Care	Simple	Breeding and age of animal	Breeding and age of animal.	Isolation from male	Simple
Injections	Simple injection.	40 injections	6 injections.	2 to 3 injections	Simple injections.
Route of Injection	Subcutaneous	Multiple injections	Subcutaneous	Intravenous	Subcutaneous
Re-use of Animal	Possible	Animal killed.	Animal killed.	Possible	Possible
Rest period after possible reaction	1 month			1 month	1 week or less; (preferably 1 week)
End reaction.	Simple observation of eggs in water.	Search for ovaries in 5 animals	Search for ovaries	Search for ovaries.	Observation of sperms in cloacal contents.

The rapidity of the A-Z test has been increased by the six-hour and 2-hour modifications of the original A-Z test but these tests, as Nieburgs [11] (1949) states, are " not reliable especially in conditions other than pregnancy, namely in women undergoing menopausal changes, in normal women for three successive days during mid-interval of the cycle with a range from the 12th to the 18th day and in men and women after coitus."

FURTHER OBSERVATIONS

Refrigeration of pregnant urine specimens indicated that after a month of refrigeration the specimen was unfit for further use and assay. The titre of the pregnancy hormone in hydatidiform mole specimens was also found to decrease gradually on refrigeration. An aequeous extract of the precipitate obtained after mixing the pregnant urine with acetone did not lose its potency after 144 hours of refrigeration, the extract injected being the concentrate from 10 cc. of pregnant urine.

Injections of different amounts of Proluton, Progynon B Oleosum mixtures of the two in different proportions and testosterone produced no spermatogenesis in *B. melanostictus*. Robbins and Parker [12] (1949) have reported that epinephrine when injected in the male *Xenopus laevis* results in producing a positive reaction. Adrenaline failed to produce a similar result in *B. melanostictus*.

DISCUSSION

Observations on *B. melanostictus* were begun in July 1949 and concluded one year later. It was found that this animal reacted to the pregnancy hormone all the year round, irrespective of whether the animal was in captivity or caught freshly.

The difficulty encountered in providing adequate food for our experimental animals has already been stressed. As no immediate solution to this difficulty could be provided we were forced to resort to starving the animals and there was no adverse effect in their reaction to chorionic gonadotropin.

Various authors have recommended the use of more than one animal for a single test and the injection of neat urine. This has resulted in a high mortality rate of their test animals. Our experience with *B. melanostictus* leads us to assert that it is safe to inject one ' standardised' animal per test with the urine concentrate as prepared by the acetone precipitation method, thereby reducing the animal mortality.

This test can be used by any hospital for the quick diagnosis of pregnancy, normal or extrauterine, and vesicular or hydatidiform mole if a supply of a few ' standardised ' toads is assured.

RESULTS AND CONCLUSIONS

Of the 124 pregnancy tests done using the toad, 60 were confirmed by the Friedman Test, of which 29 were both positive, and 31, both tests negative. Of the other 64 tests done on the toad only, 38 were positive and 26 negative.

The male toad *B. melanostictus* is a very sensitive indicator of chorionic gonadotropin and shows no seasonal variation in responding to this important hormone and as such is recommended for adoption in determining the presence of this hormone in human urine. The dorsal lymph sac route has been observed to be a better one than the others hitherto reported. For concentrating urine samples, the acetone precipitation method has been found to be very satisfactory. To avoid false reactions, the cloacal contents of the test animal should be examined at one hour intervals.

REFERENCES

1. Aznar-Ferreres, J.: Pregnancy Test Using Male Anura, Nature **168**: 881-882 1949.
2. Bach, I. and Szmuk, I.; Male Toads in Pregnancy Tests, Lancet **257**; 218, 1949.
3. Cutler, J. N.: An Appraisal of the Male North American Frog (Tana Pipiens.) Pregnancy Test with Suggested Modifications of the Original Technique, Jour Lab. Clin. Med. **34**: 554-559, 1949.
4. D'Arcy, E. N. S. and Gronwall, F. A.: A Simple Rapid Test for Human Pregnancy—The Use of the Common New Zealand Male Frog (Hyla Aurea), The New Zealand Med. Jour. **48**: 572-580, 1949.
5. Dittebrandt, M.: Use of Xenopus Laevis in Testing for Pregnancy, Amer. Jour. Clin. Path **19**: 284-288, 1949.
6. Frazer, J. F. D. and Wohlzogen, F. X.: Male-Toad Pregnancy Test, Lancet **257**: 134, 1949.
7. Haines, M.: The Male-Toad Test for Pregnancy, Lancet **255**: 923-226, 1948.
8. Haskins, A. L., Jr. and Sherman, A. I.: Quantitative Bio-Assay of Chorionic Gonadotropin in the Male Frog, Endocrinology **44**: 542-545, 1949.
9. Klopper, A. and Frank, H.: The Use of English Male Toads in Pregnancy Tests, Lancet, **257**: 9-11, 1949.
10. Ng Chung Hin, A. and Webb, J. L.: Male Toad Pregnancy Test, Lancet **257**: 539, 1949.
11. Nieburgs, H. E.: Diagnostic Procedures, Hormones in Clinical Practice, pp. 248-345, Cassell and Co., Ltd., London, 1949.
12. Robbins, S. L. and Parker, F., Jr. The Reaction of Male Frogs to Epinephrine Endocrinology **44**: 384-388, 1949.
13. Scott, L. D.: Concentration and Detoxification of Human Urine for Biological Pregnancy Diagnosis, Brit. Jour. Exper. Path. **21**: 320-324, 1940.
14. Weisman, A. T., Snyder, A. F. and Coates, C. W.: The "Frog" Test (Xenopus Laevis) as a Rapid Diagnostic Test for Pregnancy, Amer. Jour. Obstet. Gynec. **43**: 135-139, 1942.
15. Weisman, A. T. and Coates, C. W.: Frog Test (Xenopus Laevis) for Pregnancy Western J. Surg. **52**: 121, 1944

MEINICKE'S CLARIFICATION REACTION (MKR II) FOR SYPHILIS *

Pashpati Nath Wahi †

Recent studies of the venereal disease clinic of the S. N. Hospital, Agra show that the attendance of the syphilitic patients is mounting steadily. In order to root out and check this contagious disease its diagnosis should be made as early as possible, and this requires daily labotory's service. Amongst the sero-diagnostic methods Wassermann's reaction as a daily routine is a cumbersome task to do. Keeping this difficulty in view, if some test simple in procedure, equally specific and sensitive, can prove its worth, it will be of immense help to the V. D. Clinic in sorting out positive cases in the shortest possible time.

The new Meinicke's clarification reaction, which in its present form was introduced in 1932, is at least easy to perform and does not call for special equipment such as shaking apparatus, inactivation, thermostat or like. Being convenient to carry out it has in later years enjoyed increasingly wide usage.

In the State serum institute at Copenhagen, the routine tests now done are Wassermann's and Kahn's tests, and all cases showing only a trace of reaction with one or both of the two antigens are control tested with Meinicke's antigen.

The object of this paper is to submit a preliminary report on Meinicke's clarification reaction done in 793 sera and 8 cerebro-spinal fluids together with Wassermann's and Kahn's tests on similar numbers.

MATERIALS AND METHODS

Materials

Sera and cerebro-spinal fluids sent to the department of Pathology for Wassermann's reaction were also tested by Meinicke's and Kahn's antigens. The Wassermann's reaction was done once a week followed by Meinicke's clarification reaction and Kahn's test on the next day. A record was kept of the physician's clinical diagnosis together with the history of exposure if given.

METHODS

Reagents :—

1. Standardized antigen, original solution containing lipoids of ox heart, balsam of tolu and Victoria blue (A.-B. Astra, Sodertalje, Sweden.)

---

* Presented at the Annual meeting of the Indian Association of Pathologists, Agra, November, 1950.

† Department of Pathology, Medical College, Agra.

2. 3.5% solution of sodium chloride.
3. 3.5% solution of sodium chloride, containing in addition 0.01% sodium carbonate.

Apparatus :—

The reaction is carried out in small round bottomed tubes, made of glass of low alkali content and as identical as possible. Size approximately 80×9 mm. These tubes can be had from A.-B., Astra Sodertalje, Sweden. As these were not available, Kahn's test tubes and Wassermann's racks were used in the test. Only other requirements are 1 c.c. and 10 c.c. graduated pipettes, two beakers and few test tubes of 6″×¾″ size. For each serum two test tubes are used and in this way Wassermann's rack can accommodate 24 sera. Unlike serum the cerebrospinal fluid requires three test tubes for the test.

Preparation of the antigen :—

The antigen is the solution in ethyl alcohol of ether, nonsoluble lipoids mixed with balsam of tolu dissolved in ethyl alcohol (5%), and Victoria blue dissolved in ethyl alcohol (0.002%). Due to the fact that the antigen always is used in dilution of 1 in 10, it is necessary to standardize each new lot, varying the amounts of the solution of the heart lipoids and balsam of tolu. The present antigen contains in 1000 c.c. :—

Meinicke's heart extract	135 c.c.
Tolu balsam solution	370 c.c.
Victoria blue solution	100 c.c.
Absolute alcohol	395 c.c.

Technique :—

30 Gm. of powdered dry ox heart is shaken in a bottle of glass with 30 c.c. of narcotic ether for 24 hours. It is placed at room temperature for 4 days and once daily shaken by hand. The heart powder is collected by Buchner's funnel, and is washed with narcotic ether.

Once more the dry powder is treated with ether as mentioned above. After the second extraction and washing the dry powder is weighed and is extracted with 10 c.c. of absolute alcohol per Gm. The extraction takes place for 24 hours, during which time the bottle is shaken. The bottle is then placed at room temperature for 6 days and once shaken by hand. The yellowish crude, Meinicke's extract is collected by filtration.

Standardization of the Meinicke's antigen :—

6-10 mixtures of heart extract and tolu balsam are produced, all with the same concentration of Victoria blue solution.

Each mixture is tested against 6 pooled sera :

1 Negative 4 Weak 1 Strong

Table showing dilutions.

M. h. Extr. ..	2.0	3.0	4.6	2.0	3.0	4.6	2.0	3.0	4.6
T. Solu	4.6	4.6	4.6	6.0	6.0	6.0	8.0	8.0	8.0
V. Solu	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0
Alch. abst. ..	11.4	10.4	8.8	10.0	9.0	7.4	8.0	7.0	5.4
	20.0	20.0	20.0	20.0	20.0	20.0	20.0	20.0	20.0

The useful mixture (s), (or others mixed later on are) is compared with the old antigen. To accept a mixture as equal to the old antigen; it is claimed that no significant difference is found, when the testing is performed on 3 days, each day taking a new group of sera (10 negative and 10 weak positive).

Test Proper:—

The test proper consists of mixing the antigenic mixture prepared from the two salt solutions, into the patients non-inactivated serum and cerebro-spinal fluids, and leaving it at the room temperature protected from the direct sunlight, for 16 to 20 hours.

There are two different antigenic mixtures prepared each containing the antigen and the two salt solutions in 1: 10 proportion.

The amount of these mixtures depends upon the number of sera and cerebro-spinal fluids to be tested. For 21 sera and cerebro-spinal fluids 10 c.c. each of two salt solutions is taken into two labelled beakers. The antigen is measured down in 1 c.c. quantity in two test tubes separately. These test tubes should be closed with the rubber stoppers, to avoid evaporation of the antigen. The salt solutions are first heated to 55 to 56° C, and then again heated with antigen for 2 minutes. The heated salt solutions are mixed by plunging them into the antigen. The antigen with soda is now ready for use. The antigen without soda is further heated for 2 minutes in the same water bath of 55 to 56° C. The temperature is important and should be kept in the specified range of 55 to 56° C.

The antigen without soda is used in cerebro-spinal fluids while serum requires both the types of antigenic mixtures.

For serum two test tubes are arranged in a row. The tubes in the first row are expressed as belonging to the main series, and those in back row belong to the soda series. In the main series 0.2 c.c. and in the soda series 0.1 c.c. of serum is transferred. The antigenic mixture without soda and with soda are added in 0.5 c.c. quantity in the main series and soda series respectively. The tubes are shaken well and are left at the room temperature for 16 to 20 hours. Protection from the direct sunlight is to be assured.

With the cerebro-spinal fluid the test is carried out in the three tubes. The cerebro-spinal fluid is distributed in the quantity of 0.5, 0.2, and 0.1 c.c. in the first, second and third tubes respectively. In the first two tubes 0.1 c.c. of antigen without soda is added and in the last tube 0.2 c.c. antigen is measured down.

INTERPRETATION OF RESULTS

Interpretation of results differs in serum and cerebro-spinal fluid as do the test themselves. In serum test, negative sera produces in both the test tubes homogenous, bluish white opaque suspension most often with a small button of the bluish precipitate at the bottom.

Positive sera produce a more or less distinct clarification of the colloid suspension. In cases of weakly positive sera (+) the main series present an aspect of incomplete clarification. The soda series shows no clarification. Moderately positive sera (++) produce complete clarification in the main series, whereas the soda series presents incomplete clarification. Strongly positive (+++) are signified by the complete clarification and the precipitation of the colloid suspension in both the tubes. In addition to these reactions there occurs a over strong positive reaction, in which case the soda series is perfectly clear but not the main series. Such reactions can also be produced by negative sera on very rare occasions when they have been stored for a long time. These reactions disappear if the serum is diluted with a reliable negative serum, whereas overstrong reactions remain always positive.

In the interpretation of the results with the cerebro-spinal fluid the characteristic feature is the appearance of the precipitate. Complete clarification is obtained in very strong reactions. In the negative reaction, a sharply outlined blue button is formed in the centre at the bottom of all the three test tubes. This button flows out into a blue streak if the tube is carefully kept in an oblique position. With weakly positive reaction the button in the first tube is replaced by diaphanous precipitate covering the whole bottom. The precipitate cannot be made out to flow. In the other two tubes the buttons are intact. With moderately strong reaction the button in the second tube is also replaced by the above described precipitate, and with strong reactions the diaphanous precipitate appears in the third tube also. The over strong reaction forms blue precipitate in the third tube which does not flow out if the tube is tilted, while in the first or even second tube there is a blue button present.

RESULTS

Meinicke's, Wassermann's and Kahn's tests were done on blood and cerebro-spinal fluids of 768 cases. In 33 cases only Meinicke's and Wassermann's tests were performed. For purposes of analysis blood serum and cerebro-spinal fluid examinations have been grouped together as the later are few in numbers.

Analysis of the results :

TABLE 1.—*Distribution of negative and positive results in 801 sera and cerebro-spinal fluids.*

	No.	Percent.
Sera & C. S. F. giving positive results	347	43·3
Sera & C. S. F. giving negative results	454	56·7

TABLE 2.—*No. of sera and C. S. F. positive in each test.*

MKR II	W.R.	Khan's Test
249	208	202

TABLE 3.—*Results of Meinicke's, Wassermann's and Kahn's tests in 768 sera and cerebro-spinal fluids.*

	Agreement.			*Disagreement.*		
	No.	Percent.	Total percent.		No.	Percent.
Negative reactions ..	438	57	76.2	Cases	 182	23.8
Positive reactions ..	148	19.2				

TABLE 4.—*Results of Meinicke's and Wassermann's tests in 33 sera and cerebro-spinal fluids.*

	Agreement.			*Disagreement.*		
	No.	Percent	Total percent		No.	Percent
Negative reaction	16	49·6	85·9	Cases	.. 5	14·1
Positive reactions	12	36·3				

In 182 cases Meinicke's, Wassermann's and Kahn's tests were done, and in 5 cases only Meinicke's and Wassermann's tests were performed. The former have been grouped into 6 groups, and the latter into a separate 7th group, according to variation of results amongst each other.

TABLE 5.—*Analysis of the Disagreement in sera and cerebro-spinal fluids.*

Group No.	MKR II	W.R.	Kahn test	No. of cases with history of exposure.	No. of cases with clinical diagnosis of syphilis.	No. of cases in which other lesions were diagnosed but syphilis was a differential. diagnosis.	No. of sera.
1	Negative	Positive	Positive ..	Nil.	1	1	2
2	Positive	Positive	Negative	6	7	6	19
3	Positive	Negative	Positive	10	18	7	35
4	Negative	Positive	Negative	5	20	25	50
5	Positive	Negative	Negative	5	31	23	59
6	Negative	Negative	Positive	Nil.	9	8	17
7	Positive	Negative	Not done	Nil.	3	2	5

TABLE 6.—*Distribution of cases which showed disagreement amongst the three tests*

Clinical diagnosis with History.	Total cases	MKR II	W.R.	Kahn's Test
Cases with history of exposure	26	21	11	10
Cases with clinical diagnosis of syphilis ..	89	59	28	17
Cases with diagnosis of other lesions in which syphilis was a differential diagnosis ..	72	38	32	16

TABLE 6*a*.—*Disagreement in positive results with Meinicke's, Wassermann's and Kahn's test in cases clinically diagnosed other than syphilis.*

Lesions.	Total No.	MKRII	W.R.	Kahn's Test
1. Infections (bronchitis, laryngitis and osteomyelitis)	4	1	2	1
2. Chronic gonorrhoea	2	1	1	..
3. Leprosy	1	1	1	..
4. Skin diseases (Psoriasis etc.) ..	4	4	1	..
5. Eye diseases (conjunctivitis and Iriodocyclitis)	10	5	4	3
6. Neoplastic diseases	4	4	1	...
7. Abortion	28	13	12	8
8. Rheumatoid arthritis	1	..	1	..
9. Heart diseases (rheumatic) ..	2	1	1	..
10. Cirrhosis liver & amoebic hepatitis	3	2	2	..
11. Endemic Ascites	2	..	2	2
12. Chronic malaria	2	1	1	..
13. Nervous diseases (hemiplegia and paraplegia)	9	5	3	3

Total—72 cases.

Table 7.—*Comparative study of Meinicke's with Wassermann's and Kahn's tests as compared separately.*

MKR. II and W.R. (801 *Sera and C. S. F.*)

Agreement.				*Disagreement.*		
	No.	Percent	Total Percent		No.	Per cent
Negative reactions	471	58.6	80.9	Cases	151	19.1
Positive reactions	179	22.3				

Table 8.—*MKR. II AND Kahn's Test* (768 *Sera and C. S. F.*)

	No.	Percent	Total Percent		No.	Per cent
Negative reactions	488	63.5	87.3	Cases	97	12.7
Positive reactions	183	23.8				

Table 9.—*W.R. and Kahn's Test* (768 *Sera and C. S. F.*)

	No.	Percent	Total Percent		No.	Per cent
Negative reactions	497	64.7	84.1	Cases	121	15.9
Positive reactions	150	19.4				

COMMENTS

In 801 cases there were 187 disagreements which have been analysed. As the results will show that there were 26 cases in which history of syphilis was given by the patients, and out of these Meinicke's clarification reaction was positive in 21 cases. Wassermann's and Kahn's tests were positive in 11 and 10 cases respectively. Here Meinicke's clarification reaction gave more specific reactions. In 89 cases where the clinical diagnosis of syphilis was made, Meinicke's clarification reaction was positive in 56 cases Wassermann's and Kahn's tests being positive in 28 cases each. In the remaining 72 cases where the clinical diagnosis of other lesions than syphilis were made, there were 23 cases in which only Meinicke's clarification reaction was weakly positive. Clinically these cases were of abortions, paraplegias, hemiplegias, skin diseases, eye diseases, cirrhosis liver, and neoplastic diseases. All these cases denied of having had any exposure in the past. We are not in a position to express opinion about the results of Meinicke's clarification reaction in this group. May be that these are the fallacies of the Meinicke's test on the assumption that such fallacies are given by Wassermann's and Kahn's tests.

Summarising both agreement and disagreement, it will be seen that Meinicke's clarification reaction showed agreement in 76.2 per cent of cases when done together with Wassermann's and Kahn's tests on similar numbers. Compared with Wassermann's and Kahn's separately, it will be seen that it agrees more with Kahn's test than the Wassermann's test although the difference is not very great between the two comparative results. When Wassermann's test is compared with Kahn's test the agreement comes in 84.1 percent of cases.

These figures show that Meinicke's clarification reaction will at least give 76.2 to 80 per cent of correct results. The test if performed owing to its simple procedure can sort out 76.2 per cent to 80 per cent of positive and negative cases correctly. The Kahn's test although simpler to do than Wassermann's test, requires inactivation and shaking apparatus which are not at all necessary in the Meinicke's clarification reaction and this gives it a point of advantage. The Meinicke's test consists only of mixing the patient's serum with the antigenic mixture, and hence is easy and convenient to carry out requiring not much time.

Meinicke's clarification reaction can therefore be done as a screening test daily while Wassermann's test being done once a week to check the doubtful results. The little disadvantage is that the results cannot be prepared before 16 to 20 hours.

AN UNCOMMON COMPLICATION OF AMOEBIC LIVER ABSCESS

B. P. Tribedi and A. R. Roy[*]

Amœbic liver abscess is so common place as not even to interest an undergraduate, but it may assume so many diverse clinical forms, and may so cleverly masquerade as other diseases, that it is also a very common rock on which many an astute clinician has foundered. The case reported below presents some very interesting features.

CASE REPORT

A. N. D., an Indian male, aged 42 years, was admitted on the 8th March 1950 with the complaints of (*i*) pain in right hypochondrium for two months and (*ii*) constipation.

History.—He had irregular fever, lasting for a few days at a time, and interspersed with afebrile periods. For the last 9 months the maximum temperature during the febrile periods was 102° F. There was no chill or rigor with the fever. Three months previously he had an attack of acute dysentery. Two weeks after the attack of dysentery he developed jaundice. Two weeks later still, he developed pain in the right hypochondrium which persisted till admission.

Condition on Admission.—He had no jaundice, looked anæmic and the abdomen was soft and moved well with respiration. The liver was palpable, one finger's breadth below the costal margin. The spleen was not palpable. No significant physical finding was detected in any other system.

Laboratory Investigations ·

Blood (9-3-1950) Red blood cells 3,200,000 per c.mm., Hgb. 7.7 Gm. per cent. W. B. C. 8,400 per c.mm., Polymorphonuclears 58%, Lymphocytes 34%, Monocytes 6%, Eosinophils 2%.

Blood (23-3-1950) Hæmoglobin 7.8 Gm. per cent., W.B.C. 10,000 per c.mm. Polymorphonuclears 79%, Lymphocytes 20%, Eosinophils 1%.

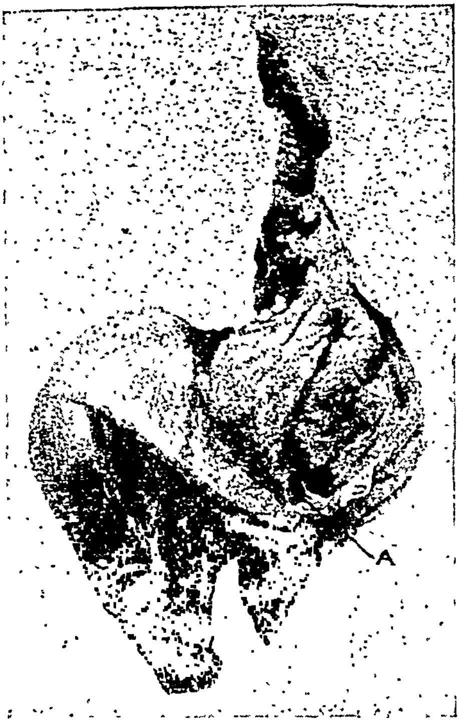
Biochemistry: Urea ..28 mg. per cent. N.P.N. ..32 mg. per cent. Sugar.. 66 mg. per cent.

Cholecystography.— "The gall bladder does not fill with the radiopaque substance, appearances suggestive of cholecystic dysfunction." In view of the past history of jaundice, pain and tenderness in the right hypochondrium, and cholecystographic findings a tentative diagnosis of chronic cholecystitis was made and the patient was operated on 8-4-1950. The gall bladder, which was approached by Kocher's incision was found diseased, and a cholecystectomy was done. (On subsequent histological examination the gall bladder showed evidences of chronic inflammation.) The patient was convalescing uneventfully when on 13-4-1950 at 4 p.m., he complained of sudden acute discomfort in the chest and collapsed. Resuscitation measures were at once instituted but inspite of all attempts he died 2 hours and 45 minutes later.

Autopsy revealed, a large solitary abscess cavity (3" in diameter) filled with chocolate coloured necrotic material in the left lobe of the liver, destroying almost the whole of the substance of the left lobe, leaving a thin shell. The abscess opened into the pericardial sac through a rent in the diaphragm (fig. 1). The pericardial sac contained about 1 pint of chocolate coloured pus. The visceral layer of the pericardium was shaggy in appearance due to deposition of greyish necrotic material. Both pleural cavities were free and clear, and there was no involvement of either lung. The only other significant macroscopic finding was the presence of 3 ulcers in the cæcum, with undermined edges and necrotic centres. No gross lesion was detected in any other part of the body. A smear prepared from the abscess wall in the liver showed numerous trophozoites of *Entamoeba histolytica*. A smear prepared from the wall of the ulcers in the cæcum showed a fair number of them. Pus from the abscess cavity in liver was sterile on cultural examination.

---

[*] Department of Pathology, Medical College, Calcutta.



Histological examination.—In sections taken from abscess area and adjoining liver tissue, the abscess cavity was found to be made up mostly of necrotic material, with some admixture of polymorphonuclears and lymphocytes, there was some fibroblastic reaction around the abscess, and fair number of trophozoites of *Entamoeba histolytica* were found in the meshes of the fibroblasts. In sections taken from other areas there was a diffuse fibroblastic proliferation of the portal spaces with round cell infiltration.

The wall of the ulcers in the cæcum showed trophozoites of *Entamoeba histolytica.*

The pericardial membrane was covered with necrotic material in the meshes of which there were some polymorphonuclears and lymphocytes. No amœbae seen. No other significant histological lesion in any other viscera was detected.

DISCUSSION.

Rupture into the pericardium occurs in abscesses of the left lobe of the liver, when it grows upwards. An abscess of the left lobe of the liver, untreated, may point anteriorly, downwards or upwards. One pointing anteriorly is recognised earlier, because it produces a tender swelling in the epigastrium. Because of the smallness of the size of the left lobe, one is quite justified in taking cognizance of the fact that even when it points upwards or downwards, a large sized abscess of the left lobe is liable to produce some amount of swelling in the epigastrium. It is astonishing to learn how large an abscess can exist in the left lobe without producing an epigastric swelling, and such abscesses may indeed escape recognition till one of them ruptures into the pericardium or left lung and/or the left pleural cavity when it points upwards, or into the stomach when pointing downwards. This particular patient was unfortunate because he did not survive the initial shock of the rupture which proved rapidly fatal, leaving no time for active treatment.

Rupture of an abscess into the pericardium and without involvement of either lungs and/or pleura is distinctly rare. A few cases, however, have been reported where in association with involvement of either lungs or pleurae or both, there was involvement of the pericardium as well. F. Kern, Jr.[2] (1945) described a case of a 17 year old negro who clinically presented the features of tuberculous pericarditis. Autopsy showed the underlying condition to be amœbic, and apart from the pericardial affection, the patient had a large amœbic abscess in the right lobe of the liver, multiple amœbic abscess in the right lung, and the right pleural cavity was affected as well. No direct connection could be demonstrated between the hepatic abscess, the pleural cavity or the pericardium. Numerous amœbae were demonstrated in all the lesions. G. Singh[3] (1946) described a case of liver abscess bursting into the pericardium. The clinical and roentgenographic diagnosis was pericarditis with effusion, liver abscess and pleural effusion, on the left side. The patient died, but unfortunately autopsy could not be done. D. Govinda Reddy and Thangavelu[1] (1948) reported a series of 9 cases of rupture of liver abscess of which 1 was into the pericardium.

In routine unselected autopsy cases in the Medical College Hospitals, Calcutta, during the last 35 years (on an average about 200 autopsies are done in a year), there were 40 cases of proved amœbic liver

TABLE I.—*Showing an analysis of amoebic liver abscess in* 6,821 *routine autopsies.*

Total number of routine autopsies	6,821
Total cases of Amoebic Liver Abscess	40
A. Site.	
Rt. lobe	26 (65%).
Lt. lobe	4 (10%).
Involving both lobes	10 (25%).
B. Number.	
Single	23 (57·5%).
Two abscesses	7 (17·5%).
Multiple	10 (25·%).

C. *Rupture.*

No rupture	31 (77·7%).
Rupture	9 (22·3)%.
Into Rt. lung & pl.	4 (44·4%).
Into Lt. lung & pl.	1 (11.1%).
Perit. cavity	2 (22.2%).
Pericardium	2 (22.2%).

abscess (where amœbae have been demonstrated in smear and/or in histological section). In this series, (Table I), there are 9 ruptures, of which 2 were into the pericardium.

REFERENCES.

1. Govinda Reddy, D. and Thangavelu, M. : Some Aspects of Amoebiasis in Madras, Ind. Med. Gaz. **93** : 557-563, 1948.
2. Kern, F. Jr. : Arch. Int. Med. **76** : 88-92, 1945.
3. Singh, G. : Amoebic Abscess of Liver Bursting into Pericardial Cavity, Ind. Med. Gaz. **81** : 299-301, 1946.

ERYTHROBLASTOSIS FŒTALIS THROUGH MATERNAL ISO-IMMUNISATION

Satyavati C. Buch *

INTRODUCTION

This is not a bibliographical review of all the literature that has accumulated on this subject but a general survey for those who come in occasional contact with stillbirths, neonatal jaundice and anæmia.

According to Sanford,[74] Erythroblastosis fœtalis can be defined as " any condition in which there exists an abnormal number of immature red blood cells in the neo-natal period......associated with a number of unlike clinical conditions occurring in the newborn period :—universal fœtal hydrops, familial icterus gravis, and certain instances of congenital anæmia caused by a hæmolytic disturbance".

The ætiology of this condition was obscure until a decade ago. In 1938, Darrow[13] attributed the disease to an antigen-antibody reaction in the fœtal system due to a serological difference in adult and fœtal hæmoglobin. The full pattern of its occurrence was worked out by Levine and Stetson[42]—that the maternal system produced antibodies to a dominant blood property present in the father, inherited by the fœtus. This theory was proved correct soon after the discovery of the Rhesus factor of blood by Landsteiner and Wiener[40] in 1940. The blood property which Levine talked of was identical with the Rh factor in a majority of cases of Erythroblastosis fœtalis. The warm irregular agglutinin found by Levine [43], [45], [46], [47] in the serum of mothers having affected infants, and by Wiener and Peters[86] in patients giving transfusion reactions with ABO compatible blood, corresponded to the immune Rh antibody prepared by Landsteiner and Wiener. The idea of iso-immunisation by fœtal factors being responsible for crythroblastosis seemed very logical, because pregnancy provides two ideal conditions for optimum immunisation, (1) slow administration of antigen and (2) action of antigen over a long period[51]. Many investigators working along the same lines found that though diseases like diabetes and syphilis, may cause the condition, the major cause responsible for this syndrome is iso-immunisation by the Rh factor, its subtypes, Hr. factors, and ABO blood groups. Even the M and P groups, which are of low antigenicity have been mentioned in this connection.

---

* The Department of Laboratories and Research, Tata Memorial Hospital, Bombay.

I Rh FACTOR

1. HISTORY: Landsteiner and Wiener[40] injected rabbits and guinea-pigs with the red blood cells of the Rhesus monkey, and with the immune serum so produced, tested human erythrocytes. Among white Americans, 85% gave positive reactions with this serum, and were known as Rh positive. The 15% *giving negative reactions* were Rh. negative. In 1941, Wiener [87] found an Rh anti-serum in a white woman which gave 70% positive results, as opposed to 85% in the original serum. He called this serum Rh'. and when he found a third Rh antiserum giving only 30% positive results [90], he designated it as Rh.'' This last serum was found independently by Race[66] in England and called KJ by him. The discovery of the Rh factor solved two important clinical problems, the cause of Erythroblastosis fœtalis and the reason for severe transfusion reactions in the absence of an apparent incompatibility.

2. NOMENCLATURE AND INHERITANCE. There are two distinct theories regarding the nomenclature and inheritance of the Rh factor, its subtypes and the Hr. factor (which has to be included here in a discussion on this subject). Wiener[92] designated the three types Rho, Rh' and Rh'' later modifying the latter two to rh' and rh'' to denote their lesser antigenicity. According to his nomenclature a combination of Rho and Rh' is Rh$_1$'', of Rho and Rh'' is Rh$_2$, of Rh$_1$ and Rh$_2$ is Rhy and a combination of the three Rh antigens is Rhz. The Rhy and Rhz are very rarely encountered, and have been found only twice each. [5], [69], [80]. The Hr factor and its subtypes, assumed to be analogues of Rh are similarly called Hro, hr' and hr''. Workers in England, however, follow Fisher's classification as described by Race[67] in 1944. Fisher assumed three antigens CDE corresponding to the Rh types and three antigens cde corresponding to Hr types related to the CDE antigens as Hr is to Rh. A comparitive idea of the two schools of nomenclature of antigens and antisera can be obtained from Table No. I.

TABLE I. *Classification of Rh—Hr. types*

Wiener.		Fisher.	
antigen	anti-serum	antigen	anti-serum.
Rho	anti-Rho	cDe	anti-D
Rh'	anti-Rh'	Cde	anti-C
Rh''	anti-Rh''	cdE	anti-E
Rh$_1$	anti-Rh$_1$	CDe	anti-CD
Rh$_1$	anti-Rh$_2$	cDE	anti-DE
Rhy	anti-Rhy	CdE	anti-CE
Rhz	anti-Rhz	CDE	anti-CDE
rh(Hro)	anti-Hro	cde	anti-d
hr'	anti-hr'		anti-c
hr''	anti-hr''		anti-e

The inheritance of any given characteristic is through submicroscopic particles called genes. These genes are situated on the loci of rod-like structures present in the nucleus of the cell—the chromosomes which are species specific. An organism inherits only two genes, one from each parent, for any given characteristic. This one gene can be one of many genic variants, any one of which can be present on the locus of the chromosome. These variants are known as allelomorphs of the genes or more simply as alleles. Before the discovery of the subtypes the theory of inheritance was simple. There were two genes Rh and rh, inherited as Mendelian dominants, Rh being dominant over rh. With the addition of the subtypes the problem became more complex. Wiener[95] postulated the presence of eight genes Rh, rh', rh", Rh_1, Rh_2, Rhy, Rhz and rh, named after the serological properties which they determine· Fisher assumed that the Rh genes were distinct and separate, though closely linked genetically. He proposed three pairs of genes Cc, Dd and Ee, corresponding to the Rh and Hr types. Genes CDE and cde were presumed to be related to each other as the blood factors M and N. When Fisher's nomenclature was published antigens d and e were mere predictions, and were found later. This put his conjecture on a sound basis, and more workers have started using Fisher's nomenclature because of its uncomplicated nature. A great deal of confusion about the two schools of nomenclature still exists. Throughout this review except when work by English authors is mentioned Wiener's nomenclature is used, as it is more familiar to workers in this country.

3. INCIDENCE OF DISEASE: Compared to the number of Rh incompatible matings the incidence of erythroblastosis fœtalis is very low. This can be explained as being due to three factors.

(a) *The capacity of the mother to be immunised.* Due to an inherited trait some women get sensitised to any antigenic stimulus more easily, and, rarely, cases have been observed where the first pregnancy has produced a high maternal anti-Rh titre. In most women, however iso-immunisation does not become apparent until the second or third pregnancy.

(b) *Heterozygous Rh-positive group of father:* Race *et al*, and Taylor[66] working with an anti-c serum (anti-hr'-called *st* by them after the person in whom it was seen) found a preponderance of homozygous Rh positive (RhRh) fathers in families with an incidence of Erythroblastosis fœtalis. If a man is heterozygous Rh-positive (Rhrh), his child might inherit the rh gene, which, combined with the maternal rh gene would make the child's phenotype (serological constitution) Rh negative, with the result, that Erythroblastosis fœtalis would not develop in that child.

(c) *Tendency to have small families.* In the usual course of immunisation, unless the mother has had Rh-positive blood transfusion, or is very sensitive to antigenic stimulation, the first child is never affected.

In some families, the disease may never appear, because the mother is very resistant to antibody formation, and if she has only two or three children, immunisation is not strong enough to cause Erythroblastosis fœtalis in them.

4. TESTS FOR Rh FACTOR:

(a) *Test Tube Method.* The technique used to-day, is modified from Landsteiner's original method. Two drops of Rh antiserum is mixed with one drop of a 2.5 percent saline suspension of test red blood cells, in a Kahn tube for one hour. Landsteiner left the tubes for two hours at room temperature, but since Levine noted that immune Rh antibody was most active at 37°C, all tests are carried out at that temperature. The reactions are read by the sedimentation at the bottom of the tube; negative bloods show a circular deposit with a smooth edge, while positive bloods show a wrinkled sediment with a wavy border. Microscopically, a positive reaction is denoted by clumping of the red blood cells.

(b) *Rapid Slide Technique:* Diamond and Abelson[18] have described a slide test in which a drop of serum is mixed with a drop of fresh whole blood from the finger tip, on a slide, warmed slightly, and the results read against a white surface or reflected light. In positive cases, a coarse agglutination appears within a few minutes, while negative blood gives a homogenous appearance. The test tube method is followed in this laboratory for mass testing, but for individual Rh factor tests, a modified slide method, with incubation at 37°C for one hour, has been found very advantageous because of quicker action, and clearly defined positive and negative results.

(c) *Capillary Method.* Chown[10] has devised a capillary tube method, mainly for detection of sensitisation, but this method has been used for determining the Rh group also. An 8 cm. long capillary tube is dipped in Rh antiserum, which is allowed to rise in the tube to 2 cm. An equal quantity of a 2.5 percent suspension of test cells in saline is added to the serum by capillary action, and the two are mixed by tilting the tube a few times. It is then inserted in plasticene at an angle of 45°, and incubated for 15 minutes at 37°C. Rh positive cells form a beaded layer along the sides of the tube, while negative cells show a smooth unbroken line. Berlin[3] used a modification of this method, sealing the tubes with petrolatum instead of inserting them in plasticene. The authors claim that it is more sensitive than the other methods. It is not very widely followed, because even with the setting up of proper controls and checks, the inexperienced worker finds it difficult to read the results. Whichever method is used, the important steps are (1) incubation at 37°C, and (2) use of sensitive controls—both Rh positive and Rh negative. Most workers use all the three types, Rho, Rh_1 and Rh_2 cells as positive controls.

5. ANTIBODIES.

(a) *Classification.* The atypical warm agglutinin that Levine [44] came across in the maternal serum in a case of Erythroblastosis fœtalis was subsequently identified as the Rh antibody. This antibody was also seen by Wiener and Peters[86] in cases of transfusion reactions. Wiener[92] could further classify this antibody into three serological types according to the Rh specificity as Rho antibody, rh'-antibody, and rh" antibody. The finding of any of these three varieties of antibody became a criterion for diagnosing a case of Erythroblastosis fœtalis, due to Rh factor. In some cases, however, even though the disease was present in a severe form, no antibody was found in the serum. Diamond[20] suggested that an antibody was present but that it was masked serologically by the presence of an inhibitor substance in the serum which prevented the agglutination phenomenon. In 1944, Race [68, 66] found a thermostable antibody which coated the cells but failed to agglutinate them. He called this "incomplete" antibody, assuming it to be similar to the antigenic haptene which combines with the antibody without giving a visible *in vitro* reaction. Wiener[94] described the same antibody independently but he called it univalent or "blocking antibody," because it saturated the surface of the red cells and "blocked" their agglutination by bivalent agglutinins. When tests for this antibody were also employed sensitisation due to Rh factor was detected in 92 percent of the cases, as compared to only 50% when only the bivalent agglutinins were known. In 1946, a third variety of Rh antibody was detected by Hill and Haberman[31]—the "tertiary" or "developing" antibody which is produced earlier during the course of pregnancy and gives very high ante-and post-natal titres. This "cryptagglutinoid" is detected by methods similar to the blocking antibody but is a distinct immuno-chemical entity, as confirmed by electrophoretic studies.[33]

(b) *Tests for the Rh antibody.*—These can be divided into three groups. These (*i*) Tests for bivalent or saline agglutinins, (*ii*) Tests for univalent blocking or "incomplete" antibody and (*iii*) Tests for tertiary or "developing" antibody.

(i) *Tests for Bivalent agglutinin.*

1. Biological test: This test was used only in transfusion cases where incompatibility, not necessarily due to Rh, was suspected. The patient's serum was withdrawn at intervals during the transfusion and any colour change, due to hæmolysis, noted. Presence of a hæmolytic reddish tinge, specially progressive as transfusion proceeded, denoted incompatibility. This is an obsolete test only of historical value.

2. Modified Tube Incompatibility Method: Equal quantities of the unknown serum and known Rh positive cells (2% suspension in

saline) are incubated in a small tube at 37°C. Presence of aggultination denotes, sensitisation. This is a non-specific test and not very reliable, as it fails to detect sensitisation in 50 per cent of cases.

3. Diamond and Abelson's [18] rapid slide technique is described in detail under tests for the Rh factor. Instead of the known Rh antiserum the unknown serum is substituted, and Rh positive cells are used. This is a very reliable test. According to Diamond in a series of 1300 investigations, it failed to detect sensitisation only in three cases.

4. Chown's Capillary Method has also been described fully elsewhere. This test is not used as a routine measure.

(ii) *Tests for Detection of Blocking Antibody:*

(1) Wiener's[88] Indirect Test: The principle underlying this test is the capacity of the blocking antibody to prevent agglutination of sensitised cells in the presence of the commonly known Rh antibody. The test is initially carried out like the tube test for Rh factor. If after one hours incubation no agglutination is seen, the cells are centrifugalised, and the supernatent saline is removed. A drop of potent Rh antiserum is added to the cells and the tube is further incubated at 37°C. Lack of clumping after incubation for 30 minutes denotes the presence of blocking antibodies. This test is out-dated now as more sensitive methods are known. To find the titre of the blocking antibody in the serum, this test is carried out using serial dilutions of the serum. The reciprocal of the highest dilution which fails to agglutinate the cells is taken as the titre of the blocking agglutinin, whereas the reciprocal of the highest dilution which agglutinates the cells, is the titre of the bivalent antibody.

2. Conglutination Test: In 1945, Wiener[96] described a new direct technique for detection of the blocking antibody. It differs from the indirect test in the substitution of plasma or compatible serum as diluent instead of saline. A direct clumping of the Rh positive cells is obtained. Wiener called this "Conglutination (Co—agglutination) to distinguish it from the clumping given by saline agglutinins, and the antibody "glutinin." This "secondary molecular adhesion" is due to the presence of a colloidal substance the—"X-protein" or "Conglutinin" in the plasma serum, and in all protein diluents. In the light of Wiener's observation Diamond explained the sensitivity of his slide technique as being due to the plasma in the drop of fresh whole blood. The conglutination test gave 92 percent positive results, the only drawback being the tendency of the erythrocytes to rouleaux formation in the presence of plasma. Diamond and Denton[19], trying out various protein media as diluents for this test found that, while plasma, horse albumin, dextrose solution were all apt to give false positive reactions, 20 percent human or bovine albumin gave clear cut reactions. In all conglutination tests albumin is the diluent of choice, the blocking antibody

also being known as "albumin antibody." If it is not available, plasma and compatible serum may be used with advantage. This test is ten times as sensitive as the indirect test.

(3) Coomb's [11], [12] Anti-Human Globulin Test or the Developing Test.

This method is based on the idea that red blood cells, sensitised by the blocking antibody, have adsorped antibody globulin on their surface. This, on addition of anti-human globulin serum, produces agglutination. Equal volumes of a 2 percent saline suspension of Rh positive cells and test serum are incubated at 37°C for an hour. If no clumping is visible, the cells are centrifugalised, the saline removed and a drop of rabbit anti-human globulin serum is added to the cells. Further incubation at 37°C for a short while produces agglutination in the presence of adsorped globulin. This test is very accurate and can be used to detect Hr—sensitisation, and *in vivo* sensitisation of the infant's cells.

(iii) *Tests for the Tertiary Antibody:* [31], [11], [12]. This antibody cannot be detected by the indirect method because it does not saturate the cells and therefore does not give a blocking reaction. It is detected by Coomb's Developing Test and by albumin agglutination. It gives reactions which are stronger and more sensitive than the other two antibodies.

(c) *Production:* Unlike α and β, Rh antibody is never found as a naturally occurring iso-hæmagglutinin of human serum. It can be produced only on immunisation of the animal system.[8], [41]. It is produced in experimental animals by injections of suitable quantities of Rh positive blood. The drawbacks are that not all injected animals yield potent sera, and often, heterospecific agglutinins interfere with the Rh specificity of the sera. The best sources for diagnostic purposes are (1) Rh negative individuals who have been inadvertently immunised by repeated transfusion of Rh—positive blood and (2) Rh negative mothers who have a high titre of Rh immune antibody through repeated pregnancies with Rh positive fœtuses.

(d) *Interpretation:* The antibody makes its appearance in the last trimester of pregnancy. If it is present earlier, it is usually a "carry over" from previous immunisation due to earlier pregnancies or blood transfusion. Immunisation during a particular pregnancy can be usually inferred from a gradual rise in the ante-natal titre of immune Rh antibody, reaching its peak within a fortnight after parturition. This is not completely specific as sometimes even when the fœtus is Rh negative, there is an anamnestic rise in ante-natal titre. No drastic steps, such as induced abortion, or Caesarian section should be undertaken by relying solely on the tite of the antibody. Davidsohn[16] found that the clinical features and prognosis of a case depend largely on the concentration of the antibody in the serum. The symptoms present, and course of disease is not dependent on the type of antibody present. Howard[36] found no "cause and effect" connection between the type of antibody and the course of Erythroblastosis fœtalis. He suggested that the blocking antibodies might be produced as a protective mechanism against the bivalent agglutinins. Davidsohn[16] states, however, that far from being protective in nature, the presence of blocking and tertiary antibodies makes the prognosis graver than if only the saline agglutinins are present. This can be borne out by the fact that sometimes in severe cases of Erythroblastosis, the bivalent agglutinin is completely absent, and the blocking antibody is solely responsible, for the extensive damage, mainly to the liver and spleen.

(e) *Duration:* Once the antibodies are formed they are present in the serum for a long time.[29] Levine[46] mentions a case where they were found two and a half years after the last delivery. They have been seen even ten years after the last delivery in one case.

6. SIGNS AND SYMPTOMS: (a) Erythroblastosis fœtalis was recognised as a clinical and pathological entity, even before its ætiology had been established. The most exhaustive survey of the disease has been given by Darrow[13] under the heading "Icterus gravis neonatorum." According to her, the most prominent symptoms are "marked jaundice present at birth, or appearing later, hepato-splenomegaly, slight or severe œdema, usually in the extremities or eyelids. The icteric index is elevated to an extreme degree, the most prominent symptom being jaundice.

(b) The blood picture shows a macrocytic, hyperchromic anæmia, and an increase in the number of nucleated red blood cells, the majority being normoblasts with a few basophilic erythroblasts. Leucocytosis is also present.

7. PATHOLOGY: There is severe and extensive extra-medullary hæmatopœsis involving mainly the liver, spleen and bone-marrow. When kernicterus is present, the brain is tinged pale yellow to a deep orange depending on the deposition of bilirubin, particularly in nuclear areas. Intracranial hæmorrhages may also be found.

8. DIAGNOSIS: (a) *Case History:* This is an important factor in the antenatal diagnosis of Erythroblastosis fœtalis. The presence of the disease in all children already born to a Rh incompatible couple, are very suggestive pointers towards a positive diagnosis of Erythroblastosis fœtalis. When marked generalised œdema due to erythroblastosis is already present, an intra-uterine roentgenogram of the fœtus is helpful in the ante-natal detection of the condition.

(b) *Presence of Antibody:* In the neo-natal diagnosis of the disease, the presence of any of the three types of antibody, in the maternal serum serves as a confirmatory finding if the clinical symptoms are already present. For the ante-natal diagnosis a rising titre is helpful in forecasting the disease, but when the father is heterozygous, it is not always indicative. As a general rule, with a previous history of the condition, and the presence of the antibodies in the maternal serum, Erythroblastosis fœtalis should be expected, and arrangements made for proper treatment.

9. MECHANISM OF ISO-IMMUNISATION: After isoimmunisation by dominant blood factors had been accepted as the causative factor, a doubt arose as to how exactly the maternal system got immunised to fœtal erythrocytic antigens. Levine[51] wrote in 1946 that "inspite of absence of direct proof of passage of fœtal red cells across the placental barrier, the statistical data on the pathogenesis of Erythroblastosis fœtalis permit no conclusion"—other than the presence of trans-placental immunisation. He suggested later[52] that the transfer of fœtal red cells into the maternal circulation and subsequent iso-immunisation takes place trans-placentally in the last trimester of pregnancy, because structural changes in the placenta make an exchange of fœtal and maternal circulations easier. This assumption also agrees with the fact that the maternal Rh antibody titre rises only during the second half of pregnancy. Wiener [98] held that immunisation took place only during labour, his argument being that nowhere had he found a case that showed antibodies in the first pregnancy except in cases of previous Rh positive blood transfusion. This assumption can be disputed because primiparae, without any history of blood transfusion have shown Rh antibody in their sera. Infants delivered by Caesarian section have also shown symptoms of typical Erythroblastosis. One point in favour of Wiener's theory, that there is a post-partum rise in titre, can be explained on the basis, that during labour, the fœtal red blood cells are forced into the maternal sinuses in large amounts, due to mechanical manipulation. Kline[39] has studied placental tissue from cases of erythroblastosis and found ample histological evidence of transplacental immunisation as the placental villi were clogged with fœtal Rh positive red blood cells.

10. PATHOLOGY: Levine's statistical proof of the pathogenesis of erythroblastosis was accepted unanimously. After the discovery of two different kinds of Rh antibodies, Wiener [98, 101] postulated a theory of differential ætiology. From a survey of 97 families he concluded that icterus gravis was caused by saline agglutinins and hæmolytic anæmia by the blocking antibody. Many workers have disputed this statement and cited cases where the blocking antibody

has been found in icterus and the saline agglutinins in anæmia. Concentration of the antibody seems to play a greater part in the pathogenesis of the two syndromes rather than the type of antibody. It is however probable that the adherence of the blocking antibody to the red cells might render them more fragile leading to hæmolysis and anæmia.

II. TREATMENT: Till 1943, treatment for this condition was not specific. If excessive blood destruction caused severe anæmia, the last resort was to transfuse blood irrespective of the Rh group. Gimson[24] transfused several cases of Erythroblastosis fœtalis with Rh negative blood, and showed a significant incidence of recovery in her cases. She recommended Rh negative blood transfusion as the therapy of choice, to be carried out soon after birth, irrespective of erythrocyte count or hæmoglobin level. Darrow[14] stated in 1945 that Rh positive blood could be given as, "with this blood there is no danger......of flooding the circulatory system, since the Rh positive blood cells, absorbing the iso-antibodies, are destroyed." This procedure does not seem a very practical therapeutic aid. If blood transfusion is to be effective, the transfused cells should survive in the system long enough to aid the body till the hæmolytic process ceases. Transfusion of Rh positive blood defeats its own purpose, as the cells get destroyed on introduction into the circulation and in no way remedy the anæmia and the resultant anoxemia.[21] According to Liber[53], the hæmolysis of blood cells might damage the kidneys severely, by the precipitation of hæmatin and thrombosis of capillaries by agglutinated cells. If the infant recovered, irreparable lesions would be left. Hence, "the hypothetic sparing action on the infant's cells is far more than counterbalanced by dangers of intravascular hæmolysis." Sanford[74] suggests the use of Rh positive blood, only if it is compatible *in vitro* at 37°C, but most physicians hesitate to introduce Rh positive blood into the infants circulation and cause an enhancement of the hæmolytic process already present. Rh negative blood is always used, and in extreme cases maternal red blood cells, washed free of all traces of serum, have been employed.

Wiener[91] has developed a technique known as exsanguination transfusion on the principle that complete removal of Rh positive blood from an affected infant, and substitution of an equal quantity of Rh negative blood would increase the infant's chances of survival. This technique is also known as " Exchange", " Replacement" or "Substitution" transfusion. Wallerstein[85] carried out the technique using the sagittal sinus for withdrawal of blood, but dangers of intra-cranial thrombosis does not allow this technique to be of routine use in the hands of an inexperienced physician. In Wiener's method, blood is introduced from the saphenous vein and removed from the radial artery, the introduction always being 50 cc. ahead of the withdrawal to prevent air-hunger. The rate of withdrawal and injection, must be approximately equal, clotting being prevented by the use of Heparin[100] (0.5 cc. before starting the transfusion and 0.5 cc. midway through the procedure). The quantity given by Wiener is 500 cc. and the amount removed is 450 cc. By this method 90 percent of the blood is replaced. The veins are usually obtained by venesection. If the transfusion is done within 8 hours of birth, the umbilical vein may be used with advantage. The exchange transfusion was originally used only in cases of severe icterus gravis, but now that the hazards accompanying the technique are minimised, it is used in all cases, where the disease is likely to appear, on the strength of the mother's case history. [54], [58] Pennell[61] transfused sedimented red cells, which technique, according to him compares favourably with exchange transfusion as the smaller the quantity of plasma administered the smaller is the risk of further hæmolysis due to enhancement of agglutinin titre.

Carter[9] prepared a lipoid substance—Rh haptene—by precipitating laked Rh positive red blood cells with alcohol and extracting it with ether. According to Carter, this substance inhibits the Rh antibodies in serum. On the basis of this property Loughrey and Carter,[55] Sanford[74] *et al.* have used the substance as a prophylactic and therapeutic measure in Erythroblastosis fœtalis, with success. Other workers[81] repeating Carter's work did not find the specific inhibitory action of the haptene. The efficacy of the Rh haptene in prophylaxis and treatment of Erythroblastosis fœtalis is still a matter of controversy.

The most recent prophylactic measure in preventing the disease is the ante-natal intramuscular administration of anhydro-hydroxy-progesterone and vitamin K, with a view to minimising uterine contractility, bleeding and early abortion. In a series of cases treated by Hoffman and Edwards[35], the disease did not develop in any of the infants. Patients who had antibodies previous to treatment showed a marked reduction or complete disappearance of antibody titre after a course of treatment. Of the three untreated control cases, antibodies were found in all three, and two of these mothers delivered affected infants. This is only a preliminary report, and has not yet been confirmed by further work.

During treatment of a case of Erythroblastosis fœtalis, it is important to bear in mind that breast feeding is definitely contra-indicated. Immune Rh antibodies have been demonstrated in colostrum by Witebsky [105], [104] *et al*, and Fisk and Foord[23]. Even when the antibodies in the infant's circulation are lessened, an introduction of further doses from breast milk would prolong the hæmolytic activity against the child's red blood cells. Whenever there is an indication that iso-immunisation might be the cause of this neo-natal condition breast feeding should not be started.

12. Erythroblastosis foetalis in India: The clinical features of the disease were recognised, but iso-immunisation as a causative factor was taken into consideration only after the incidence of Rh negative bloods was reported from various parts of India. Table II gives the percentage of Rh negative bloods, found in series of random samples by different workers.

Table II. *Percentage of Rh negative bloods of random samples by different workers.*

Investigators.	Place.	Per cent.
Khanolkar and Sanghvi[38] ..	.. .. Bombay ..	2.0
Ranganathan *et. al* [70] ..	.. .. Madras ..	4.1
Grewal *et. al.*[26]	.. .. Calcutta ..	10.0
Das Gupta [15]	.. .. Calcutta ..	10.0

Like all other inherited traits, the incidence of the Rhesus factor differs from race to race, and is used as one of the criteria for the anthropological classification of the races of mankind. The discrepancy in values obtained by these workers can be explained on the basis of the heterogenous origin of the peoples of India. In Bombay alone, Sanghvi[75] found that the percentage of Rh negatives varied widely in the different communities (Parsees 7 percent, Vadnagara Nagars 12 percent C. K. P. 8 percent, Marathas 1.5 percent.)

In 1947 Ranganathan[72], [71] reported two cases of typical Erythroblastosis fœtalis. During the same year, Sanghvi and Khanolkar[75], published their studies on the incidence of Erythroblastosis fœtalis in Bombay, and reported six cases with full serological studies. Grewal and Roy Chowdhury[27] have reported three cases, one pregnancy terminating in Hydrops fœtalis. Besides the six cases mentioned by Sanghvi, eight more cases have been investigated in this laboratory and will be published later. One is a case of feeble mindedness due to probable kernicterus, with a persistent maternal blocking antibody titre of 1/4, nine months after parturition. No other case of brain involvement has hitherto been reported in India.

In spite of the high incidence of Rh negative individuals in some communities, it is surprising that so few cases are seen. However, with gynæcologists and pediatricians in the country becoming more "Rh conscious," and with better facilities for investigation, this disease can be recognised and treated quickly, lessening considerably the high mortality rate of Erythroblastosis fœtalis.

III Rh SUBTYPES

When both parents are Rh positive iso-immunisation of the maternal system might still occur, due to subtype incompatibility. Wiener[94] has described a case of icterus gravis in which the rh' mother got immunised to the Rh_2 antigen, present in the foetus and father. An Rh_2 antibody could be demonstrated in her serum. Waller[84]*et al* report two cases of Rh_1 immunisation. Atypical anti-Rh_1 was present in both the cases. The first child, who was Rh_2 like the mother was not affected by the disease. Cases due to rh" factor seem to be occurring oftener than due to rh' and have been reported by various authors.[79].

In spite of the mother being Rh positive, the therapy in subtype iso-immunisation is Rh negative blood. If Rh positive blood is used, the subtype might be incompatible and cause needless complications.

IV Hr FACTOR.

According to Fisher's hypothesis, there should be three anti-sera reacting with antigens, c.d.e, or in Wiener's terminology—hr', hro and hr": Levine[45] found an anti-Hr serum in an immunised mother with an affected child. This serum agglutinated all Rh negative and heterozygous Rh positive bloods." Wiener[97] noted its serological similarity to rh' and called it anti-hr' (anti-c). Race and Taylor[82] found a similar serum *st* which also reacted like Levine's anti-Hr serum, but gave 80 per cent positive results. Anti-sera against d and e antigens were encountered by Mourant[59] and Diamond. This made the Hr series complete. Genetically it is related to the Rh series like the MN groups.

The Hr factor is much less antigenic than the Rh factor. Very few cases of iso-immunisation have been mentioned in connection with Erythroblastosis fœtalis. Besides the case where Levine first reported the serum, he[46] mentions two more cases of Erythroblastosis fœtalis due to Hr. factor. Race [82] *et al* have reported a case. Hill and Haberman[32] mention a case of Hro immunisation in a pregnant woman, with the production of active saline Hro antibody. It is interesting to note that in most cases of Hr immunisation mentioned in literature, more often the cause has been multiple transfusions rather than pregnancy.[96]

V ABO BLOOD GROUPS.

A significant number of cases of Erythroblastosis fœtalis were encountered where the Rh factor the subtypes and Hr factors could be excluded as immunising agents. Further investigations on these cases of unknown aetiology, led workers to conclude, that the ABO blood groups, were responsible for the disease. Under certain conditions, the naturally occurring iso-agglutinins α and β could be produced as immune antibodies and cause a syndrome identical to Erythroblastosis fœtalis produced by Rh factor.

1. CRITERIA FOR DIAGNOSIS: Three main criteria should be fulfilled before a case can be diagnosed as due to iso-immunisation by the ABO groups. (1) Heterospecific pregnancy, (2) Exclusion of other blood factors and (3) Abnormally high titre of maternal iso-hæmagglutinin against the fœtal blood group.

(a) *Heterospecific pregnancy:* As early as 1928 Hirzfeld [34] mentions ABO heterospecificity in connection with late and early fœtal deaths. According to him a compatible or homo-specific pregnancy is one where the blood groups of the parents are identical or where the mother has the dominant group. An incompatible or heterospecific pregnancy is one where the mother lacks the antigen A and B, one of which is present in the father and the affected child. He did not refer to any antigen-antibody reaction as the concept of iso-immunisation by a dominant factor being a cause for the disease, came much later. Levine[48] in a statistical study of the causes of spontaneous abortions lists ABO heterospecificity as one of the factors involved. His work showed that in the white population of the United States, the ratio of compatible to incompatible matings is 65 percent: 35 percent while in matings which have resulted in two or more cases of Erythroblastosis fœtalis or fœtal deaths due to an unknown cause, this ratio is significantly higher. Halbrecht[30] found 60 cases of icterus simulating the classic neo-natal condition in a survey of 10,000 cases. The percentage of heterospecific pregnancies in these cases was 95 percent while in a group of 2,000 normal child births it was only 26.5 per cent. Halbrecht called this type of icterus, due to ABO factors "Icterus neonatorum precox" to distinguish it from icterus gravis neonatorum due to Rh factor.

Polayes and Ohlbaum [63], McNally [65], Tisdall [83], Wiener [103], Levine[48] Davidsohn[17] *et. al,* Aubert[2], have observed cases where women have given birth to erythroblastotic infants with identical Rh groups as their own. The only discrepancy was in the ABO blood group, the infant having the dominant groups. Their observations show that heterospecificity is an essential condition for classifying a case of Erythroblastosis fœtalis under ABO iso-immunisation.

(b) *Exclusion of other blood factors:* In the majority of cases investigated, the Rh group and subtype of the mother and infant are identical. In one case reported by Polayes[63] the mother was Hr negative and the child Hr positive, but no atypical anti-Hr agglutinin was found in the maternal serum. Gurevitch[28] *et. al* describe two cases where there was a double incompatibility of Rh and ABO antigens. When such a case occurs, an important diagnostic aid is the titre of the different types of antibodies.

(c) *Titre of maternal iso-agglutinin titre against the foetal ABO blood group:* Levine[48] noted that when the antigens A and B act as immunising agents, the tire of the corrsponding antibody in the maternal serum has a very significant rise. In nine cases of group O mother immunised by Group A infants, seen by Polayes[63], the titre in every case was above 1/700, in some cases going up to 1/1280. These titres seem abnormally high as compared to the average titre of 1/58 in fifty

O group nulliparae, and 1/215 in fifty O mothers of normal babies. Tisdall[83] has reported a titre of 1/16,380 in Group A immunisation of a Group O mother. Cases of B group immunisation have also been observed.

These maternal titres are strongly suggestive of specific immune antibody production, as they are very much above the range of natural iso-agglutinins. It has long been a matter of debate whether ∝ and β can act like the immune Rh antibody and cause Erythroblastosis fœtalis. The serological data available leads one to conclude that when produced by artificial antigenic stimulation to the maternal system, ∝ and β, produced as immune antibodies, act in a manner similar to the Rh antibody and cause *identical neo-natal disorders.* In a case where the titre was within normal limits(1/52) Wiener[103] found univalent ∝ blocking antibodies and ascribed the condition to conglutination of the fœtal cells.

The mechanism of iso-immunisation is similar to that of Rh factor.

2. SYMPTOMS: Clinically and pathologically the disease is indistinguishable from that caused by Rh factor. It is assumed to run a milder course, but fatal cases have been encountered. Yannet and Libermann[107], and Wiener[103] report subsequent mental retardation in severe cases which recovered. The ∝ antibody can also cause congenital anæmia lasting for a long time after birth, according to Smith[77].

3. TREATMENT: Blood transfusion of a compatible group is *the only therapy. If free antibody is still present in the fœtal system,* washed group O cells, or blood absorbed by Witebsky's A and B substance can be used.[103].

It does not seem necessary to carry out routine ante-natal titrations for ∝ and β as is done for Rh sensitisation. However, in a case of Erythroblastosis fœtalis, if the Rh and Hr factors can be excluded as immunising agents, a serological investigation of the ABO blood groups as a possible cause seems essential.

VI MN AND P TYPES.

Though M, N are always present in human erythrocytes separately or together, M and N antibodies are not regularly occurring components of serum, like ∝ and β. These blood types are never taken into account for transfusion purposes, because they are much less antigenic than ABO or Rh factors. Some workers, Callander and Race,[7] Allot and Holman[1], /Wiener,[88] Patterson [60] *et al* Phansomboon [62] *et al* have come across anti-M or anti-N antibodies during difficulties in cross-matching or in routine serological check-up during pregnancy. Bowley[6] describes two cases where anti-M was present during pregnancy. In one case the titre rose gradually during the last trimester. There was no subsequent Erythroblastosis fœtalis however, the rise in titre being purely anamnestic. Mcfarlane[57] cites a case where a group N mother with a group M infant had a case history of neo-natal deaths and anti-M in her serum. The only normal child was group N like her, suggesting thereby that the irregular M antibody was responsible for the Erythroblastosis fœtalis in the siblings. All the investigators agree however, that the M and N antibodies met with, could not have been immune antibodies, but were naturally occurring. The basis of their assumption is that when transfusion or iso-immunisation involved Rh positive blood, no antibodies were seen against this highly antigenic factor; so it was not likely that the feebly antigenic MN type could cause immunisation. According to Boorman and Dodd,[4] immune antibodies show an enhancement of titre in protein media as compared to their titre in saline. The M and N antibodies did not show a rise in titre in serum diluent, which is an important point in classifying them as non-immune antibodies.

Anti-P has been found by Wiener[88], and by Dunsford[22] in a case of transfusion reaction and in two cases of pregnancy. A case of anti-P has been found in this laboratory also. This was also classified as a naturally occurring agglutinin on the same basis as the MN antibodies.

In the case of MN and P factors, the occurrence of antibody does not seem a criterion for expecting the pregnancy to terminate in a case of Erythroblastosis fœtalis, probably because all these three antibodies are cold agglutinins giving good reactions at 4° C and 20° C, and little or no reaction at 37° C. Frank cases of Erythroblastosis fœtalis with an involvement of these three blood types are yet to be met with.

REFERENCES.

1. Allot, E. N., Holman, C. A.: Anti-N and Other Low Temperature Agglutinins in Human serum, Lancet 2: 130-131, 1947.
2. Aubert, E. F., Cochrane, J. B., Ellis, M. E.: An Unusual Case of Erythroblastosis Foetalis, B. M. J. 2: 648-649, 1945.
3. Berlin, R. R.: Determination of Rh-antibodies and Blood Grouping by the Capillary Method—Amer. J. Cl. Path. 17-233, 1947.
4. Boorman, K., Dodd, B.: Activation of Haemagglutinins by Human Serum, J. Path. & Bact. 59: 95—104, 1947.
5. van den Bosch, C., : The Very Rare Rh Genotype Rhy (C d E/cde) in a Case of Erythroblastosis Foetalis, Nature: 162-781, 1948.
6. Bowley, C. C., Dunsford, I.: Agglutinin Anti-M Associated with Pregnancy, B. M. J. 2: 681-684, 1949.
7. Callendar S. T., Race R. R.: Serological and Genetical Study of Multiple Antibodies Formed in Response to Blood Transfusion in a Patient with Lupus Erythematosus Diffusis, Ann. Eug. 13: 102-117, 1946.
8. Carter, B. B.: The Production of Rh Antiserum in Guinea Pigs Through Inoculation with Human Red Blood Cells, Amer. Jr. Cl. Path. 15: 278-279, 1945.

9. Carter, B. B.: Preliminary Report on a Substance which Inhibits Anti-Rh Serum, Amer. Jr. Cl. Path, **17** : 647-649, 1947.

10. Chown, B.: A Rapid, Simple and Economical Method for Rh Agglutination, Amer. Cl. J. Path. **14** : 114, 1944.

11. Coombs, R. R. A., Mourant, A. E., Race, R. R.: Rh Factor—Detection of Weak and Incomplete Rh Agglutinins—New Test,—Lancet, **2**: 215-16, 1945.

12. Coombs, R. R. A., Mourant, A. E., Race, R. R.: A New Test for the Detection of Weak and Incomplete Rh Agglutinin, Brit., Jr. Exp. Path. **26** : 255-266, 1945.

13. Darrow, R. R.: "Icterus Gravis Neonatorum" Arch. Path, **25** : 378-417, 1938.

14. Darrow, R. R.: Erythroblastosis Foetalis-Treatment, J. A. M. A. **127** : 1146-1147, 1945.

15. Das Gupta, C. R.: Rh Factor in Indians, Ind. Med. Gaz. **37** : 372, 1944.

16. Davidsohn, I., Stern, K.: Interpretation of Rh. Antibodies, Amer. J. Cl. Path., **18** : 690-699, 1948.

17. Davidsohn, I., Kashiwagi, G.: Foetal Erythroblastosis due to A.B.O. Incompatibility, Proc. Int. Med. Chicago, 17 : 243, 1949.

18. Diamond L. K., Abelson, N. M.: Demonstration of Anti-Rh Agglutinins—Accurate and Rapid Slide Test, Jr. Lab. & Clin. Med. **30** : 204-212, 1945.

19. Diamond, L. K., Denton R. L.: Rh Agglutination in Various Media with Particular Reference to the Value of Albumin, J. Lab. Clin. Med. **30** : 821-830, 1945.

20. Diamond, L. K., Abelson, N. M.: Rh Inhibitor Substance—Importance in Anti-Rh Serums,—J. Cl. Invest. **24** : 122-126, 1945.

21. Diamond, L. K., Denton, R. L.: Comment on Darrow's Article on Treatment of Erythroblastosis foetalis (14), J. A. M. A. **128** : 686, 1945.

22. Dunsford, I.: Agglutinin Anti-P in Pregnancy, B. M. J. **1** : 15-16, 1949.

23. Fisk, R. T., Foord, A. G.: Further Observations with the Rh Agglutinin—Studies on an Anti-Rh Serum of Unusual Specificity—Presence in Breast Milk, Amer. J. Clin. Path. **14** : 431-436, 1944.

24. Gimson, J. D.: Haemolytic Disease of the Newborn-Treatment with Rh-Negative Blood, B. M. J., **2** : 293-297, 1943.

25. Grewal, S. D. S., Chowdhery, A. B. R.: The Rh Constituent of Human Red Blood Cells, J. I. M. A. **13** : 65, 1943.

26. Grewal, S.D.S., Chowdhery, A.B.R., : Rh Negative Rate of Indians, Nature, **157** : 411, 1946.

27. Grewal, S. D. S., Chowdhery, A. B. R., Mukherjee, N. C. : Three Cases of Isoimmunisation Against Rh Factor Found in Five Weeks Search in Calcutta Hospitals, Ind. Med. Gaz. **83** : 370-372, 1948.

28. Gurevitch, J., Polishuk, Z., Hermoni, D.: Rh Incompatibility in Hetero-specific Pregnancy, Amer. J. Cl. Path. **16** : 574-579, 1946.

29. Halac, E., Garzon, H. L.: Isoimmunisation Against the Rh Factor—Studies on the Duration of its Activity, Ann. Pediatrics (Basel) **172** : 317, 1949.

30. Halbrecht, I.: The Role of Haemagglutinins α and β in Pathogenesis of Jaundice of the Newborn (Icterus Neonatorum Precox) Amer. J. Dis. Child **68**: 248-249, 1944.

31. Hill, J. M., Haberman, S.: Demonstration of Rh Antibodies in the Newborn and Further Evidence of Erythroblastosis Foetalis, J. Lab. Cl. Med. **31**: 1053-1065, 1946.

32. Hill, J. M., Haberman, S.: Two Examples of Sera Containing Anti-d Predicted by Fisher and Race, Nature **161**: 689, 1946.

33. Hill, J. M., Haberman, S., Guy, R: Further Evidence of Antibodies of the Third Order, Amer. J. Cl. Path. 19: 134, 1949.

34. Hirzfeld, L.: Konstitutionserologie und Blutgruppen-forschung" Berlin. J. Springer: as cited by Levine P. (46) 1928.

35. Hoffman, R. B., Edwards, D. P.: New Concept in the Treatment of Rh-Negative Pregnant women—A Preliminary Report, Amer. J. Obs. Gynae. **59**: 207, 1950.

36. Howard, J., Lucia, S. P., Hunt, M. L., McIver, B. C.: Clinical Significance of Rh Antibodies in Sera of Rh-Negative Mothers, Amer. J. Obstet. and Gynaec. **53**: 569-595, 1947.

37. Hubinont, P. O.: Isoimmunisation by Blood Group Factors ABO. in Man, B. M. J. **2**: 574-575, 1949.

38. Khanolkar, V. R., Sanghvi, L. D: Distribution of Rh Factor in Indians. Nature, **155**: 427, 1945.

39. Kline, B. S.: The Pathogenesis of Erythroblastosis Foetalis, Blood, **4**: 1249-1255, 1949.

40. Landsteiner, K., Wiener, A. S.: Agglutinable Factor in Human Blood Recognisable by Immune Sera for Rhesus blood, Proc. Soc. Exp. Biol. and Med. **43**: 223, 1940.

41. Landsteiner, K., Wiener, A. S.: Studies on a Human Agglutinogen Recognised by Immune Sera for Rhesus Blood, J. Exp. Med. **74**: 309-320, 1941.

42. Levine, P., Stetson, R. E.: An Unusual Case of Intra-group Agglutination, J. A.M.A. **113**: 126-127, 1939.

43. Levine, P., Katzin, E. M.: Isoimmunisation in Pregnancy and Varieties of Isoagglutinins Observed, Proc. Soc. Exp. Biol. and Med. **45**: 343-348, 1940.

44. Levine, P., Katzin, E. M., Burnham, L.: An Atypical Warm Agglutinin, Proc. Soc. Exp. Biol. and Med. **45**: 346-348, 1940.

45. Levine, P.: Discovery of the Hr factor"—Year book of Path. and Immuno, pp. 508, 1941,

46. Levine, P., Katzin, E. M., Vogel, P., Burnham, L.: Pathogenesis of Erythroblastosis Foetalis, Science: **94**: 371-372, 1941.

47. Levine, P., Katzin, E. M. Burnham, L.: Isoimmunisation in Pregnancy—its Possible Role in the Pathogenesis of Erythroblastosis Foetalis, J.A.M.A. **116**: 825-827, 1941.

48. Levine, P.: Serological Factors as Possible Causes in Spontaneous Abortion, J-Hered. **34**: 71-79, 1943.

49. Levine, P.: The Pathogenesis of Erythroblastosis Foetalis, J. Pediat. 23: 656-675, 1943.

50. Levine, P.: Mechanism of Iso-immunisation by the Rh Factor of Red Blood Cells, Arch. Path. 37: 82-90, 1944.

51. Levine, P.: The Present Status of the Rh Factor, Amer. J. Cl. Path. 16: 597-620, 1946.

52. Levine, P.: Mechanism of Transplacental Immunisation, Blood. 3: 404 413, 1948.

53. Liber, A. F.: Comment on Darrow's Article on Treatment of Erythroblastosis Foetalis (14), J.A.M.A. 128: 686, 1945.

54. van Loghem J. J., van Bolhius, J. H., Soeters, J. M., Veerneklaas, G. M. H.: Treatment of Erythroblastosis Foetalis with Replacement Transfusions, B. M. J. 2: 49-53, 1949.

55. Loughrey, M.D., Carter, B. B.: The Treatment of Severe Erythroblastosis Foetalis with Rh Haptene, Amer. J. Obs. Gynaec. 55: 1051-1052, 1948.

56. Majumdar, D. N.: Rh Frequency in the People of Lucknow, Heredity. 2: 399-401, 1948.

57. McFarlane, M. N.: Anti-M Agglutinin in Human Serum, B. M. J. 2: 883-884, 1945.

58. Molony, C.: Treatment of Erythroblastosis,—Calif. Med. 72: 89-90, 1950.

59. Mourant, A. E.: A New Rhesus Antibody, Nature 155: 542, 1945.

60. Patterson, J. L. H., Race, R. R., Taylor, G.: A Case of Human Isoagglutinin Anti-M, B.M.J. 2: 37-38, 1942.

61. Pennell, S.: Treatment of Erythroblastosis Foetalis by Transfusion with Sedimented Cells, Blood 5: 107-122, 1950.

62. Phansomboon, S., Ikin, E. W., Mourant, A. E.: Human Serum Containing Anti-N Agglutinin, Lancet: 2: 285, 1949.

63. Polayes, S. H., Ohlbaum, C.: Erythroblastosis Foetalis Unrelated to the Rh. Factor, Amer. Cl. Path. 15: 467-470, 1945.

64. Polayes, S. H.: Erythroblastosis foetalis in Mothers with Rh *Positive Blood* Report of Six Cases with Comments on Iso-immunisation by A & B Agglutinogens, Amer. J. Dis. Child 69: 99-102, 1945.

65. Polayes, S. H., McNally, Jr.: Isoimmunisation with A and B Factors, and its Relation to Haemolytic Disease of the Newborn,: Amer. J. Clin. Path. 18: 375-386, 1948.

66. Race, R. R., Taylor, G. L., Boorman, K., Dodd, B. S.: Recognition of Rh Genotypes in Man, Nature. 152: 563-564, 1943.

67. Race, R. R., Taylor, G. L., Cappel, D. F., McFarlane, M. N.: Recognition of Further Common Rh Genotypes in Man, Nature 153: 52-53, 1944.

68. Race, R. R., Taylor, G. L.: The Incomplete Antibody in Rh Immunisation,—B. M. J. 2: 756, 1944.

69. Race. R. R. Taylor, G. L.: Serological Reactions Caused by the Rare Human Gene Rhz, Nature 155: 112-113, 1945.

70. Ranganathan, K. S., Ramachandra Rao C. S., Ratnakannan, N. R.: Incidence of Rh Factor in Indians, Nature 157: 411, 1946.

71. Ranganathan, K. S.: A Typical Case of Iso-immunisation Against the Rhesus Factor, Ind. Med. Gaz. **82**: 269-272: 1947.

72. Ranganathan, K. S.: Heterozygous Transmission in a Large Family with a Case of Erythroblastosis Foetalis, Ind. Med. Gaz. **82**: 404-406, 1947.

73. Ranganathan, K. S.: Rh-Hr Types in South India—Incidence, J. I. M. A. **17**: 162-165, 1948.

74. Sanford, H.: Erythroblastosis Foetalis, Med. Cl. N. Amer. **34**: 187-200, 1950.

75. Sanghvi, L. D., Khanolkar, V. R.,: Erythroblastosis Foetalis in Bombay Ind. J. Med. Sc. **1**: 45, 1947.

76. Sanghvi L. D., Khanolkar, V. R., : Data Relating to Seven Genetical Characters in Six Endogamous Groups in Bombay, Ann. Eug. **15**: 52-64, 1949.

77. Smith, C. H.: Chronic Congenital Anaemia Associated with Immunisation with A Blood **4**: 697-705, 1949.

78. Snyder, L. H.: Rh Factor and Feeblemindedness, J. Hered. **36**: 9-10, 1945.

79. Steven, E. M.: Pure Anti-E Antibody in the Serum of a Rh Positive Woman Lancet **1**: 447, 1950.

80. Stratton, F.: Rh Antibodies in Human Sera—a New Variety, Nature: **153**: 773, 1944.

81. Stratton, F., Renton, P. H.: The Rh Haptene, Lancet **1**: 326, 1950.

82. Taylor, G. L., Race, R. R.: Haemolytic Disease of the Newborn—Preponderance of Homozygous Rh-Positive Fathers, B. M.J. **1**: 288-289, 1944.

83. Tisdall, L. H., Hartnett, E. T.: Erythroblastosis Foetalis Due to Blood, Group ABO Imcompatibility, —N. Y. State J. Med. : **149**: 1699-1701, 1949.

84. Waller, R., Levine, P., Garrow, I.: A Case of Erythroblastosis Foetalis Caused by Immunisation of an Rh Positive Mother by the Rh Factor,—Amer. J. Cl. Path. **14**: 577, 1944.

85. Wallerstein, H.: Treatment of Severe Erythroblastosis by Simultaneous Removal and Replacement of the Blood of Newborn Infant, Science **103**: 583-584: 1946.

86. Wiener, A. S., Peters, H. R.: Hemolytic Reactions Following Transfusions of Homologous Blood, with Three Cases in Which Some Agglutinogen was Responsible,—Ann. Int. Med. **13**: 2306-2322, 1940.

87. Wiener, A. S.: Hæmolytic Reactions Following Transfusions of Blood of the Homologous Group, Arch. Path. **32**: 229-250, 1941.

88. Wiener, A. S.: Hæmolytic Transfusion Reactions: III Prevention, with Special Reference to the Rh and Cross-Match Tests, Amer. J. Cl. Path. **12**: 302-311, 1942.

89. Wiener, A. S.: Distribution and Heredity of Variants of the Rh. Type, Science 98: 182-184, 1943.

90. Wiener, A. S., Sonn, E. B.: Additional Variants of the Rh Type Demonstrable with a Specific Human Anti-Rh Serum, J. Immunol: **47**: 461-465, 1943.

91. Wiener, A. S., Wexler, I. B., Gamrin, E.: Hemolytic Disease of the Fetus and New Born Infant, with Special Reference to Transfusion Therapy and the Use of Biologic Test for Detection of Rh Sensitisation, Amer. J. Dis. Child, **68**: 317-323, 1944.

92. Wiener, A. S.: Nomenclature of the Rh. Blood Types. Science, **99**: 532-533, 1944.

93. Wiener, A. S.: Rh factor—Role of Subtypes in Haemolytic Transfusion Reactions and in Erythroblastosis,—Amer. Jour. Cl. Path. **14**: 52-60, 1944.

94. Wiener, A. S.: A New Test for Rh Sensitisation, Proc. Soc. Exper. Biol. and Med. **56**: 173-176, 1944.

95. Wiener, A. S. Sonn, E. B., Belkin, R. B.,: Heredity of the Rh Blood Types, —Jour. Exp. Med. **79**: 235-253, 1944.

96. Wiener, A. S.: Rh Sensitisation Conglutination Test,—Jour. Lab. Cl. Med. **30**: 662-667, 1945.

97. Wiener, A. S.: Hr. factor—Theory and Nomenclature, Science: **102**: 479-482, 1945.

98. Wiener, A. S.: Notes on the Pathogenesis of Congenital Haemolytic Disease, Amer. J. Cl. Path. **16**: 1 319-321, 1946.

99. Wiener, A. S.: Pathogenesis of Erythroblastosis Foetalis-Statistical Evidence,. Amer. Jour. Cl. Path. **16**: 761-767, 1946.

100. Wiener, A. S., Wexler, I. B.: Use of Heparin when Performing Exchange Transfusion in Newborn Infants, Jour. Lab. Cl. Med. **31**: 1016-1919, 1946.

101. Wiener, A. S.: Congenital Haemolytic disease, and Erythroblastosis Foetalis —Two Disease Syndromes N. Y. State J. Med. **46**: 912-913, 1946.

102. Wiener, A. S., Peters, H. R.: Intra Group Incompatibility Due to hr Factor, Amer. J. Cl. Path. **18**: 533-536, 1948.

103. Wiener, A. S., Wexler, I. B., Hurst,: The Use of Exchange Transfusion in the Treatment of Severe Erythroblastosis Due to ABO Sensitisation, with Observations on Pathogenesis of the Disease, Blood **4**: 1014-1032, 1949.

104. Witebsky, E., Anderson, G. W., Heide, A. D.: "Demonstration of Rh Antibody in Breast Milk (in Relation to Erythroblastosis Foetalis), Proc. Soc. Exp. Biol and Med. **49**: 179—183, 1942.

105. Witebsky, E., Anderson, G. W., Heide, A. S.: Demonstration of Rh Antibody in Breast Milk (in Relation to Erythroblastosis Foetalis—Further Investigations), Proc. Soc. Exp. Biol. & Med. **52**: 280-281, 1943.

106. Wintrobe M. : On the Nomenclature of Anti-Rh Typing Serums, Science **107**: 27-30, 1948.

107. Yannet, Lieberman,: Mother-Child ABO Incompatibility—A Relation of Socreter Status to Mental Deficiency, Amer. J. Dis. Child **79**: 176-183, 1948..

REPLACEMENT TRANSFUSION IN ERYTHROBLASTOSIS FOETALIS

A Case Report *

Satyavati C. Buch † **and G. D. Adhia** ‡

The diagnosis and treatment of Erythroblastosis foetalis are still in the early stages of development in India. Only one instance of treatment of this neo-natal condition by replacement transfusion has been reported in India, in the lay press. It is felt that this report will prove of interest, because besides presenting an unusual case, it describes a modified technique of blood transfusion, which allows for rapid introduction and simultaneous withdrawal of blood without citrate intoxication and putting an excessive load on the cardio-vascular system.

CASE HISTORY.

Mrs. R. S. H., a Hindu,Deccani lady aged 35, married for 20 years. First full term delivery resulted in the birth of an infant with icterus gravis neonatorum. The infant had epistaxis and bleeding from the mouth and died two and a half weeks after birth of severe jaundice. Fifteen years later, she gave birth to a full term normal male infant weighing 6¾ lbs. Serological examination of the parents' and infant's bloods warranted by maternal obstetric history of severe jaundice in the first born, gave the following results :—

Father S. H. Group O Rh+ve
Mother R. S. H. Group A Rh—ve
Baby Group A Rh+ve

The maternal serum showed no bivalent or blocking immune Rh antibodies.

On the fourth day after birth, the infant developed icterus, hæmoglobinurea and drowsiness. A blood picture revealed no erythroblasts. This however is no conclusive evidence of absence of erythroblastosis. Instances have been cited where cases of Erythroblastosis fœtalis with proved immunisation have given a negative blood picture. Albumin titrations for detection of immune tertiary Rh antibodies could not be carried out. Judging from the presence of icterus gravis neonatorum in the first baby, the presence of tertiary antibodies was not considered unlikely. Hence it was decided to treat this case as one of Erythroblastosis fœtalis due to Rh immunisation. A replacement transfusion with group O Rh—ve blood was carried out on 13-1-51 six days after the infant's birth. 400 c.c. of blood was introduced, and approximately 350 c.c. withdrawn. There was immediate improvement in the infant's colour specially in the conjunctivæ and sclera. The patient had a mild transient rigor shortly after transfusion. Jaundice deepened slightly after 24 hours, but cleared up eventually, along with the other symptoms of hæmoglobinurea and drowsiness. The infant progressed well and made an uneventful recovery.

---

* The author (G.D.A.) in collaboration with Dr. K. T. Gajjar has successfully done another replacement transfusion on a Bohri child on 25-5-1951 at New Hospital for Women and is grateful to Drs. Dossibai J. R. Dadabhoy and Gool. N. Vazifdar for referring the case.

† Dept. of Pathology & Research, Tata Memorial Hospital, Bombay. 12
‡ Hon. Asst. Surgeon, K.E.M. Hospital, Bombay. 12

Tests. The three blood samples were tested for the ABO and Rh blood groups and detection of sensitisation. As ABO homospecificity between the mother and infant was established, no further antibody titrations were needed.

Rh. Factor. A modification of Diamond and Abelson's Rapid slide technique was used. A drop each of known Rh antiserum, and 2.5 percent saline suspension of test cell sample was mixed on a slide kept in a moist petri dish. Results were read one hour after incubation at 37° C. Rh positive cells gave a coarse macroscopic agglutination. Rh negative erythrocyte sample RSH gave a smooth homogeneous surface without any microscopic clumping.

Tests for detection of sensitisation. (1) Saline antibody:—Serial dilution of the test serum RSH were made upto 1/64, each tube containing 1/15th c.c. of diluted serum. An equal amount of known Rh+ve homologous erythrocytes was added to each tube. Results were read after incubation of the racks holding the tubes at 37°C for one hour. No agglutination was present in any dilution from 1/1 to 1/64. This denoted the absence of the immune bivalent Rh antibody. The same titration set up for the saline antibody was used for the blocking antibody test by Wiener's indirect method. The basis of this was that if blocking antibody was present, exposure at 37°C for an hour would have already coated the Rh positive erythrocytes. After the absence of bivalent agglutinins was recorded, the tubes were centrifuged and supernatent saline discarded. A drop of known Rh antiserum was added to each tube. Results were read after re-incubation of the rack at 37°C for one hour. Strong agglutination was seen in all dilutions. This proved the absence of the univalent blocking antibody.

Technique of replacement Transfusion.—The replacement of the infant's blood was carried out by a modification of the usual technique. This rapid method has been used by author (G.D.A.) in about 23 out of 53 transfusions given to a child (aged 3 years 5 months) affected with Cooley's anæmia. 360 c.c. of blood was introduced in 25 minutes without the child showing any symptoms of cardiac embarassment or citrate intoxication. In a replacement transfusion, as the rates of introduction and withdrawal of blood are controlled, there is no risk of cardiac distress.

The infant was immobilised by a modified crucifixion splint. The long saphenous vein at the right ankle was exposed under local anæsthesia using 2.0 percent Novocaine. Two No. 0000 catgut ligatures were passed round the vein. Lower ligature was pulled, the vein cut with fine-pointed scissors, a 19 gauge cannula was inserted in the vein, ligatures tied and glucose saline infusion started. The apparatus was so assembled by the introduction of a Y-tube in the system, so as to allow a change-over from glucose saline infusion to blood transfusion without disturbing any connections. The radial artery in the lower end of the forearm was exposed. However as a 20 gauge cannula could not be negotiated even on completely cutting the artery, the artery was tied up and the wound closed.

The left brachial artery was exposed in the cubital fossa, and a 19-gauge cannula put in. The cannula was connected to a graduated blood bottle by attaching a metal sinker at the other end of the rubber tube so that the quantity of blood removed could be calculated.

After blood started coming out of the brachial artery, transfusion of citrated group O Rh negative blood was started. To cope with the rapid rate of withdrawal, the introduction was done under positive pressure of filtered air in the bottle. Although an accurate ratio of blood transfused and removed was available earlier during the transfusion, only an approximate estimate was possible after the arterial cannula slipped out accidentally. The rate of replacement was then controlled by three factors, the patient's pulse rate, colour and the approximate rate of outflow of blood.

A total of 400 c.c. of O Rh—ve blood was given while approximately 350 c.c. withdrawn. At the end of the transfusion the vessels were ligated and the wounds closed. No anticoagulant except sodium citrate in transfused blood was used throughout this procedure.

If substitution transfusion is carried out within 48 hours of birth the umbilical vein is the most convenient route, both for introduction and withdrawal of blood, the method described here, has been found satisfactory for infants who are a few days old.

SUMMARY

1. A case of Erythroblastosis foetalis due to Rh immunisation is presented.

2. A successful case so treated is reported.

The authors are grateful to Dr. Y. N. Ajinkya for referring the case to them for necessary investigation and treatment. The transfusion was carried out by one of the authors (G.D.A.) at Dr. Ajinkya's Nursing Home.

INDIAN CANCER SOCIETY

INAUGURAL MEETING

The Hon'ble Rajkumari Amrit Kaur, Minister for Health, Government of India, inaugurated the Indian Cancer Society in Bombay on the 2nd of May, 1951 in the presence of a distinguished gathering at the Taj Mahal Hotel, Bombay. The aims and objects of the Society were adopted and a Managing Committee with representatives from the different parts of India was nominated. It is expected that the Indian Cancer Society would play an important role in the campaign against cancer in this country. The two addresses delivered at the inaugural meeting are reproduced below:

INAUGURAL ADDRESS

By

Hon'ble Rajkumari Amrit Kaur,
Minister for Health, Government of India.

Allow me at the outset to thank you sincerely for giving me an opportunity to associate myself with your efforts to launch a concerted attack on one of the most dread diseases to which the human frame is subject.

Cancer is not a new disease as references to this malady can be found in ancient medical literature both of the East and of the West. I am given to understand that reliable statistics of cancer mortality are not available in many countries of the world. In India where the cause of death is recorded mostly by laymen, our figures are of little or no value. Cancer morbidity statistics in India are also incomplete and insufficient to allow us to make any generalised statements on the incidence of the disease in different parts of the country or on its comparative frequency in the table of morbidity from all causes. There is a general impression that the incidence of cancer in India is much less than in the more prosperous and industrialised countries of the West but I understand the work of your investigators in this city has demonstrated that our people are just as much liable to this disease as people else where. It is quite possible that the commoner sites of cancer in the body may differ from the pattern prevalent in some of the Western countries but the fact remains that cancer is one of our major health problems. As public health measures continue to eliminate many of the preventable diseases such as malaria, tuberculosis, typhoid and cholera, cancer will begin to assume an increasingly dominant role in our health problems. Such has been the experience in most of the Western countries where, inspite of dynamic advances in hygiene, and in social and environmental conditions, cancer has continued and still continues its relentless march until today it occupies a very high place in their mortality statistics. We should therefore be forewarned by the experience of others and start working straightway against a scourge which is knocking at our very doors.

Although during the past 50 years, in particular the microscope, the X-ray and radium, the culture-plate of the bacteriologists, the surgeon's knife and the physician's medicaments have all helped to relieve to an amazing extent the physical ailments of suffering humanity and added greatly to the sum total of our knowledge about the causative factors of various diseases, there are still many other maladies of which we as yet know very little. Heredity, environment, occupation, social habits and economic status have all been put forward as factors influencing the causation of cancer. Are we aware as to how these factors play their respective roles in shaping the incidence and pattern of the disease in this country ? I have been told that constant chewing of tobacco and 'pan' is responsible for a particular type of cancer of the mouth and the wearing of the dhoti for another on the body. All these factors need careful investigation.

It is commonly believed that once a person is afflicted with any type of cancer there is no hope for him and that he is doomed to a slow and agonising death. This is a very incorrect opinion. Much of the mistaken notions about the incurability of cancer are due to the unfortunate fact that in India victims of cancer very often seek competent medical advice only after the disease has advanced beyond the stage of medical aid. I have been assured by knowledgeable persons that cancer is much more amenable to treatment, provided it is diagnosed early, than many other illnesses which afflict the human body and concerning which there does not appear to be such a haunting fear in the minds of people. It is high time that an organised effort was made towards removing some of these misconceptions which do exist in the minds of men about cancer. Wide publicity should be given to the fact that the occurrence of a painless lump or thickening especially in the lip, tongue or the breast, any sore on or near the tongue, mouth or lips which behaves in a refractory way to proper treatment, persistent hoarseness of voice or change in size or colour of a birth mark or mole, need thorough medical examination as any one of these signs may be an early manifestation of cancer in the body. In this programme of popular education, stress should also be laid on the fact that cancer is one of the few diseases in which treatment on proper lines yields the most satisfactory results provided the disease is discovered in its early stages. The ignorance of simple facts about cancer even amongst educated persons is appalling and this ignorance can be removed only by persistent and proper efforts. I have been told that in some of the advanced countries physicians insist on such of their clients as are in their forties and above, to undergo a periodical check-up against cancer so that the disease, particularly where its origin is in inaccessible sites, may not remain undetected for long.

Some people complain and probably rightly too, that in this country we have not done as much to combat this disease as we have done for some of the other health problems. It cannot be denied that facilities for efficient treatment of cancer are extremely inadequate for the needs of this country. There are only two institutions devoted entirely to the diagnosis and treatment of cancer. Teaching hospitals are making a heroic effort against enormous odds to organise tumour clinics besides conducting their routine work. But how should we organise a concerted attack against this particular menace to health under the conditions existing in the country? That is the question we have to pose to ourselves. There has been a tendency in the past to leave all such efforts in the hands of governmental or semi-governmental agencies and to adopt an indifferent attitude in the matter. This may not be. That society alone progresses and remains contented whose members are always awake and alive to any danger within. Your city is to be congratulated for having taken the lead in building and maintaining a cancer hospital entirely from non-governmental sources. The munificent endowment from the Sir Dorabji Tata Trust has made the Tata Memorial Hospital what it is, the foremost institution in India for the alleviation of suffering from cancer. The Trust has, I believe, already spent more than 75 lacs on capital and recurring expenditure for this one hospital and I only wish that other philanthropically minded persons or Trusts would emulate this noble and worthy example and step into the arena for the combat against cancer.

I am happy that my Ministry has been taking an active interest in the matter and we have with the courtesy and co-operation of the Sir Dorabji Tata Trust, been able to establish at the Tata Memorial Hospital the Indian Cancer Research Centre. This centre is indeed fortunate that it has, at its helm of affairs one who has earned international reputation by his contributions to the study of cancer. I should like to take this opportunity of congratulating him for the work he has done and for the universal recognition he has received for it. This centre is still in its infancy but I have every confidence that in the near future it will develop into a premier institution for postgraduate training and research in cancer.

It appears to me that an essential phase of any cancer control programme is the maintenance of a system of proper record of relevant events whereby the problem can be scientifically approached and evaluated. Your society will earn the gratitude of us all if you can organise a central bureau of information pertaining to cancer statistics, treatment and research. This information should be available to any one who seeks it. I would like to lay particular stress on the necessity for the dissemination of information from an authentic source such as yours, in order to prevent the exploitation of mistaken beliefs and notions by unscrupulous persons for base personal ends. Advertisements for so called specifics and cures lure away the unfortunate sufferers at the crucial early stage when the disease may be curable under competent advice. This must cease.

I am glad that the organisers of your Society have come forward with a broader and more active objective. Such wider outlook is absolutely essential, because we do not yet know what causes cancer and until we discover this, it is probable that much money and organised effort may be unprofitably spent. I understand that you have three basic objectives :—

1. To encourage and support the scientific search for the causes of cancer and for "the final answer" in its prevention and control.
2. To save lives by creating a public awareness of curability of early cancer and a medical awareness of the best methods of detection, diagnosis and treatment.
3. To give encouragement and volunteer aid to persons suffering from cancer.

I have no doubt that these are the right ideals to guide you in your work. I am confident too that with the help of your society we shall be able to build up an edifice of hope and confidence which may eventually mean the vanquishing of another foe to humanity. I am therefore very happy to inaugurate the Indian Cancer Society and wish it the same marked success which your sister organisations abroad such as the American Cancer Society and the British Empire Cancer Campaign have had and continue to have.

REMARKS

by

Dr. V. R. Khanolkar,

President,

International Cancer Research Commission

Cancer is the most aggressive of all the ills which mortify the human body. Upto a certain stage of its evolution it is curable by modern methods of treatment. Beyond that stage nothing that we know of to-day makes any difference to its relentless and malignant course. Our only hope in dealing with cancer lies in improving the material and the means at the disposal of those who are asked to detect and treat cancer and still more in creating a consciousness in the people about its existence and its nature.

The campaign against cancer cannot be left to organisations consisting only of official personages and experts. It has to be taken up by all the people, because no one can claim to be safe from an attack by cancer. Age, sex, economic condition and social environment do not seem to alter its general incidence. In the field of cancer control, the active co-operation of all the people is indispensable because the interest of the individual merges with the interest of all the people. An organised effort towards its eradication is therefore the concern of everyone of us. This is the main reason for starting a Society, which is intended to be as broad based as possible and which it is hoped will extend its sphere of appeal and activity to the remotest village of our country. I therefore venture to think, that to-day, a great step forward has been taken in the fight against a terrible scourge by the inauguration of an Indian Cancer Society, and we could congratulate ourselves that the highest and the lowest in our land have thought it fit to help us in our endeavour.

I have often been asked recently, why is it necessary to start a separate organisation to combat cancer? Would not the usual public health measures be adequate to meet this menace?

Permit me to explain some of the reasons:

(1) The first reason lies in the very nature of the disease. Cancer is not contagious. It is not caused by a microbe or an extraneous animal parasite. Cancer is an unrestrained and uncoordinated growth of one or other tissue of our own body. The usual methods of controlling infectious diseases are therefore ineffective in the case of cancer. All this makes the treatment of cancer much more difficult. The difference between a cancer cell and a normal cell is small as compared to that between a microbe and a tissue cell. It has therefore been relatively easy to discover natural

or synthetic agents which would kill the invading micro-organism without at the same time seriously damaging the healthy tissues. Cancer on the other hand is flesh of our own flesh and it takes a much training and very costly appliances to devise means which would destroy the cancer cells without at the same time greviously mutilating the adjacent tissues.

(2) The second reason lies in the normal evolution of cancer as different from that of any other disease. Most diseases have a tendency to be self limited. In a very large proportion of illnesses the natual resources of the body are able to arrest the spread of disease and to effect an ultimate repair. The efforts of physicians and surgeons only assist or accelerate a natural process. This explains why so many cults, systems and cures can flourish alongside of modern medicine. The progress of Cancer if left to itself, is ruthless, unrelenting and inexorable. In the large mass of information which is now available there is hardly any authenticated record of a spontaneous cure of cancer. It is therefore imperative that treatment, efficient-treatment should be instituted as soon as cancer has been detected in any part of the body. Any vacillation or temporisation in this respect invariably leads to a fatal and agonising termination. Not only is it necessary to initiate, treatment as soon as possible, it is equally important that the treatment should be well planned and carefully executed. This is clearly seen in the results recently published in U.S.A. The overall 5 year cures from all types of cancer in that country have been calculated as 30%. In many places they do not exceed 10%, while in best centres the cure rate is between 35 and 40%. This marked difference is the result of better organisation and more expert training of the medical staff at the centres.

Many of us who see so much avoidable misery and suffering along with boundless courage and fortitude every day of our life, feel very strongly on the matter of proper detection and cure of cancer. We feel that there should be a place in every regional centre where unbiassed, authoritative and uptodate information would be available to all persons who may be sufferers from cancer or who may be interested in the fight against it. We also feel that we should do everything in our power to combat quackery, both in our ranks and outside them. I am sure that if the people who publish reports about miraculous cancer cures were to observe the distress and frustration which follow their search for the sensational, they would relent in their baneful activities and help us in enlightening the general public. A good deal of the misery and suffering in our patients proceed from misinformation and misguidance. A good deal of this is unintentional and follows from ignorance. We believe that a Cancer Society can attain our objectives most effectively and economically.

And now permit me to say a few words regarding the finances which are the crucial consideration for establishing and maintaining this Society,

As you know the governments of most countries have many important and vital problems confronting them to-day. The people of other countries have therefore realised that a more effective fight can be conducted against cancer by forming active non-official organisations. Let me give you some examples from three countries. I take a small country first. Sweden with a population about twice that of city of Bombay started a National Anti-Cancer Society last year. They aimed at obtaining for this purpose one Swedish Kroner annually (which is roughly equal to one rupee) from every person of mature age. Their aim was to collect 1½ million Swedish Kroners every year. During the last year they started their appeal by way of an experiment and Prof. Berven informs me that they were able to collect 900,000 Kroners in a very short time and without much trouble. If such a scheme could be made workable in Bombay it would be possible to conduct two Tata Memorial Hospitals without much trouble.

2. The British Empire Cancer Campaign has been in existence for almost 30 years. The income for the year 1949—which is the year of the latest report—was £176,400. This collection was made during a period of unprecedented stress and strain in the country. It included donations, collections and legacies. The British Empire Cancer Campaign have allocated roughly £152 thousand out of this amount as grants to hospitals and research workers.

3. And now, let me tell you the results of work in a very active and vigorous country. The American Cancer Society during the last 12 years of its existence has collected 34½ crores of rupees. The country has been spending about 6½ crores of rupees annually in its cancer campaign. During the last 5 years the Cancer Society has spent roughly 9 crores of rupees on Cancer Research.

I am mentioning these figures to give you a rough idea as to what could be achieved by correct initiative and efficient organisation. It might be objected that the U.S.A. is a very rich nation, and that we are a very poor country. That may be so, but we were both of us crown colonies 175 years ago and our potentialities are still a matter for speculation.

ANATOMICAL SOCIETY OF INDIA.

The Anatomical Society of India was formed in Calcutta on Sunday the 20th May 1951. There was a conference held at the central lecture theatre of the Calcutta Medical College, attended by about 200 delegates and other medical scientists who came from various parts of India and Burma. It was presided over by Dr. M. N. Bose, Principal, R. G. Kar Medical College, Calcutta and inaugurated by Dr. B. C. Dasgupta, Director of Health Service, West Bengal. Dr. P. Chatterjee Prof. of Surgery, Calcutta Medical College, welcomed the delegates as Chairman of the Reception Committee. He said that anatomy and physiology were the basic subjects on which the superstructure of the medical sciences were built up and anatomy was the back-bone of all surgery. The need for the formation of the Anatomical Society of India could not be overemphasised. Messages of goodwill from eminent anatomists of U.K., U.S.A., Sweden, France, Italy and the Far East were read out. The President delivered a neat speech stressing on the importance of anatomy as a basic medical study and dwelling on the methods of better teaching of the subject and need for greater devotion to researches in anatomy. He also emphasised the co-ordination of post-graduate work in different institutions building up of good museums and reference libraries, co-operation with sister organisations in other countries and determination of Indian anatomical data and standards. He expressed his strong opinion against reduction of the present curriculum of anatomy in the preclinical course and observed that the premedical course in zoology should deal very much more thoroughly with vertebrates, specially mammals, than at present.

Dr. B. C. Das Gupta inaugurating the Society said that its formation would go a great way to help investigation and teaching of anatomy. He assured that the anatomists were sowing today a seed that was destined to grow up in course of time into a big tree with all the benefits that such an institution could offer.

Dr. A. Ananthnarayana Ayer expressed the satisfaction that a step in the right direction had been taken by the anatomists of India.

The Meeting was followed by an informal meeting of the prospective members of the Society in which the draft constitutions and rules that had previously been drawn up were discussed and amended. In the afternoon in the 'Open Session' of the Society the constitution was adopted formally and the members were duly registered.

The Head Quarters of the Society was located for the present at Calcutta. The following office-bearers were elected :—

President	..Dr. A. A. Ayer. (Madras).
Vice-Presidents	..Dr. S. R. Nair,(Bombay) and Dr. B. N. Basu, (Calcutta).
General Secretary	..Dr. S. K. Basu, (Calcutta).

Joint Secretary .. .. ..Dr. (Miss) L. Chacko, (Vellore).
Treasurer .. ..Dr. D. P. Banerjee, (Calcutta).

An Executive Committee of 12 members were formed as follows :—

Dr. M. Pan, Dr. S. C. Sinha, and Dr. S. Bagchi, (Calcutta) Dr. J. D. Warma, (Assam), Dr. Dharam Narayan, (Lucknow), Dr. T. P. Sinha (Patna), Dr. R. Mahanti, (Cuttack), Dr. P. C. Pate (Jaipur), Dr. N. S. Sahasrabuddhe (Nagpur), Dr. G. M. Kurulkar (Bombay), Dr. Y. Appajee (Mysore), Dr. V. Sitarama Rao (Guntur).

The Journal Sub-Committee was formed in this meeting.

The venue of the meeting of 21st May was at the R. G. Kar Medical College. Two interesting and largely attended synopsia were held in the morning session (1) Methods of teaching of anatomy (2) Co-ordination of researches in anatomy.

In the afternoon there was a Scientific Session in which 9 short papers were read and discussed with exhibition of some anatomical specimens. In the evening at the Bengal Immunity Hall of the Calcutta Medical Club, the Society had invited the public to witness a very interesting exposition by Prof. Bishnu Ghosh and his pupils of the "External Anatomy of the human body as influenced by the Yogasana system of physical culture". This was followed by a popular lecture on the "Pedigree of Man and Human Dignity" by Dr. A. A. Ayer.

CURRENT MEDICAL LITERATURE

MEDICINE

CORONARY HEART DISEASE, Maurice Newman: The Medical Press, **225**: 207-212 1951. 14 references.

In recent years there has been a great increase in the prevalence of coronary disease, that is angina pectoris and coronary thrombosis, better termed cardiac infarction. This increased incidence has been ascribed to the increased accuracy of diagnosis, hereditary predisposition of the disease, aeging of the population and the changing social life and habits in the present era, with the increase of intellectual occupations involving mental work with heavy responsibilities. As the basic lesion in coronary disease is atheroma, the incidence increases with age, the commonest incidence being between 50 and 70 years of age. However Newman and Yater *et al* have collected many cases of coronary disease between 18 and 39 years. All observers agree that cardiac infarction is more common in males than females, the ratio being 3.5 to 1. Tobacco has been blamed for the increased incidence in men but latest reports conclude that smoking has little, if any, influence on the prevalence of coronary disease. An accurate diagnosis is essential for the correct treatment of coronary heart disease. A careful history taking is much more important than physical examination as there may be no evidence of any abnormality on clinical examination, and the diagnosis will rest entirely on the symptoms alone. The cardinal symtom of coronary disease is pain in the front of the chest. It is central; the further the pain is from the middle line, the less likely is it to be of organic origin. Sometimes the pain is epigastric thereby giving rise to difficulty in diagnosis. It may radiate down one or both arms, into the neck or jaw. The pain may vary in degree from slight discomfort, to most intense agonising pain with the fear of impending death. It may be described as oppressive, constricting, numbing, burning, sharp, aching *etc.* Angina pain is provoked by effort. If the same amount of effort gives rise to constant substernal pain or even discomfort and disappears with rest, one can diagnose coronary obstruction even in the absence of any abnormal findings and even with a normal E. C. G. Every patient with chest pain should have an E. C. G. taken. A normal E. C. G. does not exclude coronary disease. An acute cardiac infarction is characterised by severe pain, dyspnoea and shock. The pain may be very intense and prolonged; the dyspnoea usually soon becomes manifest with or without pulmonary oedema, and Cheyne Stokes breathing may occur. There may be a sudden onset of auricular fibrillation. Shock is evidenced by weakness, a small rapid pulse, pallor with cold sweats, and a low blood pressure. The temperature is often raised for several days. The sedimentation rate is increased and a leucocytosis occurs. The E. C G. shows the characteristic changes in the T and Q waves and elevation or depression of the ST segement. In the past there has been the tendency to take too grave a view of the prognosis of coronary disease, but nowadays it is not so. The average mortality rate is 24 per cent. The prognosis is worse in the younger age groups. In an actual attack of cardiac infarction, if the pain is severe and prolonged and does not respond to morphine injections, and if the attack is accompanied by symptoms of shock with a low blood pressure, the prognosis is grave and the patient is unlikely to get better. Subsequent to an acute attack, the size of the heart is an useful guide. If the heart remains of normal size, or only very slightly enlarged, the prognosis is good, whereas if the heart is enlarged, the outlook is not so favourable. Another guide to prognosis is the pulse pressure, a low pulse pressure being unfavourable. Recovery depends on the size of the infarct, if it is small, full functional recovery may be perfect, but if the infarction is large full functional recovery will not occur and expectation of life is shortened. About 50 per cent of cases of cardiac infarction recover and have no symptoms and are able to resume full time employment. The treatment of coronary disease is immediate and convalescent. The first action is to relieve pain by injecting a 1/4 gr. of morphia hypodermically. If the pain persists another dose may be given in half an hour and a further similar dose may be administered in another half an hour if the pain still persists. The prognosis in this case will be bad. When the pain is severe morphine may be given intravenously. Morphine must be given until the pain is relieved. Oxygen should be given liberally when there is cyanosis which may also relieve pain. When the acute pain has subsided phenobarbitone 1 gr. two or three times a day may be given for restlessness and insomnia. In cases of sudden collapse with feeble pulse and low blood pressure, adrenalin subcutaneously is sometimes beneficial. Where there is peripheral shock, almost pulseless and no blood pressure reading, and no obvious signs of pulmonary congestion, intravenous plasma might save life. In attacks of syncope, due to low blood pressure and slow heart rate, and typical Stoke Adams attacks, due to heart block, adrenalin 0.3 to 0.5 c.c. of 1 in 1000 solution should be given two hourly for 48 hours, provided it is beneficial. After the emergency ephedrine ½ gr. thrice daily may be given to prevent further attacks. The practitioner has a tendency to overtreat the patient with drugs and the author therefore discusses the value of other drugs used in coronary disease. Atropine should not be given along with morphine as it increases the cardiac rate unfavourably. Digitalis is of value only when congestive failure or auricular fibrillation sets in. Quinidine is another drug that is not indicated in uncomplicated cardiac infarction. It is valuable in auricular flutter, auricular fibrillation and ventricular tachycardia, when the heart rate suddenly becomes rapid—180 to 240. A prelimnary small test dose for toxicity may be given after which 30 to 35 gr. a day in divided doses is administered. With regard to the coronary vasodilators, aminophylline and khellin, their efficiency is still controversial. Aminophylline may be given in tablet form 1.5 to 3 gr. three to four times a day. Khellin is said to be four times stronger than aminophylline and is given orally in tablet form containing 50 or 100 mg. each, three times a day. It is said to be non-toxic even after prolonged administration. A new approach in the treatment of acute cardiac infarction are the anti-coagulants, dicoumarol and heparin. They have reduced the death rate largely by reducing the incidence of thrombo-embolic complications which directly or indirectly result in death. With the advent of preparations of "depot" heparin, treatment can now be carried on at home. A concentrated aeqeous solution of heparin, 25,000 units per c.c. for intramuscular injection is now available. An initial dose of 37,000 units of heparin, followed by 25,000 units should be given. The author advocates anti-coagulant therapy in all cases of cardiac infarction except in hæmorrhagic conditions as severe anæmia, pregnancy, peptic ulcer and hepatic or renal disease. Shute of Canada has obtained good results with alpha tocopherol (vitamin E) 400 mg. intramuscularly daily, followed by 400 mg. orally in divided doses for 10 to 21 days. Another preparation advocated is choline which is given in doses of 10 to 20 Gm. daily by mouth. It is thus difficult to assess the value of any particular drug in coronary disease. During convalescence the patient must be in bed for a minimum period of six weeks. The rest must be absolute for the first three weeks; he should not be allowed to read or write or even feed himself as arm exercises increase the heart rate. When there is pulmonary œdema and congestion, the patient will be more comfortable if allowed to sit in a chair with the feet hanging down. In this position the heart has less work to do than in the recumbent position. The diet should be light and fluids should be restricted to 2 to 3 pints a day. If there is any evidence of congestive failure a salt free diet should be given. Smoking should be prohibited for at least the first few weeks. When the patient is well he must be told about the condition of his heart. He must be explained that with time his heart will get stronger and stronger. During rehabilitation the patient may be allowed to carry out exercises short of breathlessness or pain. He should be encouraged to get back to work and lead a normal life as soon as possible.

ERIC COELHO

THE MODERN TREATMENT OF SUBACUTE BACTERIAL ENDOCARDITIS, Parkinson, J. S.: The Medical Press, 225: 321-324, 1951.

Subacute bacterial endocarditis is an infection of the heart, usually of one or more valves, caused by *Streptococcus viridans* in 90 percent of cases. The remaining are due to a wide variety of organisms, the least uncommon being *H. influenzae* and the *gonococcus*. The affected heart is rarely a previously normal one, either having some congenital defect or an acquired abnormality, usually rheumatic valvular disease. The mitral or aortic valve alone is the commonest site of infection or the two together. Infections of the right side of the heart are less common and less easy to diagnose, as the shedding of the emboli in this case occurs into the pulmonary circulation and shows itself usually by recurrent pleurisv or hæmoptysis.

A good deal can be done to prevent the onset of subacute bacterial endocarditis by careful and regular supervision of potential candidates. All individuals who are known to have congenital heart disease or valvular disease of the heart should have all foci of sepsis attended to *e.g.*, carious teeth, apical abscess, septic tonsils, sinus infections, etc. Any conservative line of treatment for these conditions should be done under penicillin cover by giving 600,000 units of procaine penicillin for two days. The general health must be kept at as high a level as possible and multivitamin preparations should be given during winter. The early recognition of the onset of subacute bacterial endocarditis is very important, and any falling off in general health or the development of unknown pyrexia or any alteration of heart murmurs, demands a full overall. A blood culture should be taken if there is the least doubt. It should be kept in mind that in subacute bacterial endocarditis affecting the right side of the heart, systemic emboli are uncommon.

Penicillin is the sheet anchor of treatment of subacute bacterial endocarditis. Blood culture should be taken in all cases, and repeated several times if necessary. A high colony count, over 50, means a worse prognosis generally speaking. Treatment must not be differed if a culture is negative, but penicillin should be instituted at the earliest possible moment if it is clinically diagnosed. With the recent introduction of delayed action penicillin, such as procaine penicillin, treatment has been made less cumbersome. Procaine penicillin 500,000 units twelve hourly intramuscularly for 28 days should be given. When crystalline penicillin is used 1,000,000 units per day, divided into three hourly doses, should be administered. With this routine the temperature returns to normal within a few days, the various peripheral pains subside, the spleen shrinks and becomes unpalpable, and the petechiae cease to appear; sometimes the petechiae reappear after the temperature has become normal. After this the patient should remain afebrile and feeling well for the rest of the course of treatment. After a case has had a full course of penicillin treatment the patient should remain under observation in bed for atleast two weeks. As chances are there of relapse, it is advisable to keep a watch on the patient for a year atleast. Some patients are insensitive to penicillin and present a difficult problem. In such cases dihydrostreptomycin 1 to 2 Gm. in divided doses twelve hourly should be given for 28 days. Prior to the use of penicillin, the sulpha drugs were administered but the results were not so gratifying as penicillin. Heparin is now usually given along with penicillin and it is supposed to prevent the formation of thrombotic vegetations, to dissolve small ones and to make the organisms more susceptible to the particular therapy used. The dose usually given is 100 to 200 mg. daily over 10 days. Blood transfusions do have an occasional place in treatment when the case is very anaemic. The diet in the acute febrile phase should be light, fluids may be called in for. As the temperature settles down, normal diet should be allowed. Surgical treatment has a definite place in cases of subacute bacterial, endocarditis which occur in association with patent ductus arteriosus. The complications usually arising are heart failure, renal involvement, peripheral emboli and aneurysm formation. When there is an evidence of heart failure at the start of treatment, the prognosis is worse and if it develops during treatment it is even worse. The treatment of this complication is the same as in congestive heart failure. When the kidney gets involved red blood cells appear in the urine. The treatment is to render the urine alkaline. When peripheral emboli appear in the arteries where there is collateral circulation there is nothing to worry but when it occurs where there is inadequate alternative circulation, embolectomy must be resorted to. The development of mycotic aneurysm is not uncommon. Usually it occurs early, before treatment or in the first few days of treatment. This condition calls for surgical intervention.

The over-all figures of recovery rate is 60 percent. The earlier the case is diagnosed the better the prognosis. Those in whom the treatment is commenced within the first month of illness the recovery rate is 95 percent. This figure drops to 54 percent in cases where treatment has been delayed for more than three months. The age of the patient also makes a difference. Friedbey has found a recovery rate of 78 percent in cases under 40, and 53 percent over this age. A positive blood culture means a better chance of recovery than a negative report.

With penicillin treatment the toxic reactions are uncommon. A very small minority of cases have urticarial reaction or pyrexia. This is relieved immediately with antihistaminic drugs. Ear deafness and giddiness following streptomycin do occur but they disappear on decreasing the dosage.

ERIC COELHO.

HAEMOPHILUS INFLUENZAE MENINGITIS TREATED WITH STREPTOMYCIN, DIFFICULTIES IN DIAGNOSIS, Allibone, E.C., Pickup, J. D. and Zinnemann.: The Lancet, **160**: 610-613, 1951. 4 tables, 7 references.

The authors report 11 cases treated at the Leeds Streptomycin Clinical Trials Centre in the last two years illustrating some of the difficulties of early diagnosis. The presenting symptoms suggesting an involvement of the central nervous system were shown in only 5 of the 11 cases; 3 had gastro-enteritis and 2 were affected with an upper respiratory tract infection. In 4 of the histories there were antecedent manifestations probably having some bearing on the subsequent development of the disease. One of them had a persistent cough for a month before admission, another was hospitalised for 15 days with an upper respiratory infection, prior to final admission, while the remaining 2 cases had a head injury. Of the

11 cases, 7 were severe and 4 moderately ill. All the 4 moderately affected were cured; of the 7 severe, 3 died, 3 were cured and 1 developed dementia, blindness and hydrocephalus. The average duration of illness before admission was 6 days. The average period between admission and first lumbar puncture was 2.5 days. The necropsy in 3 cases were similar, in that, the spinal cord and both the cerebral hemispheres were encased in tenacious, yellow-green pus. In all cases the strains of *H. influenzae* isolated were type *b*. None of them were resistant to streptomycin. The authors point out that when upper respiratory infections are prevalent it is not possible to detect that a feverish cold might mean a more serious infection. Still more difficult is it to revise an established diagnosis. On the other hand, meningism and convulsive phenomena should be accorded the respect that their possible aetiology warrants. The authors endorse the plea that in any case of fever accompanied by meningeal irritation earlier and more frequent lumbar punctures must be resorted to if the results are to be improved.

ERIC COELHO.

EFFECT OF STREPTOMYCIN ON VESTIBULAR FUNCTION, Bignall, J. R., Crofton, J. W., and Thomas, J. A. B.: B. M. J. 1: 554-559, 1951. 4 tables, 26 references.

The authors investigated the effects of streptomycin on the vestibular apparatus in 76 cases under treatment for pulmonary tuberculosis. All patients were treated for at least 12 weeks and some for 32 weeks. Sixty-five were given streptomycin alone, 23 receiving 2 Gm. daily in doses of 0.5 Gm. six-hourly, 13 receiving 1 Gm. daily in doses of 0.25 Gm. six-hourly, and 19 having 1 Gm. daily in a single injection. Four patients received 2 Gm. daily in doses of 0.5 Gm. six-hourly during alternate weeks and 6 were given the same dosage during alternate months. The patients were examined at weekly intervals and more frequently if toxic symptoms were present. Vestibular function tests were carried out in 50 patients. The writers came to the conclusion that the patients receiving 2 Gm. of streptomycin a day complained of giddiness almost four times more than those receiving 1 Gm. and the giddines in these cases was first noted significantly earlier. Nystagmus and abnormalities in the caloric tests were often associated with a complaint of giddiness. Clinical tests for co-ordination of movement were useful only when there was gross ataxia, minor degrees of which were difficult to interpret in patients who were confined to bed. The authors observed that giddiness and nausea showed a tendency to occur in the same patients, and at about the same time. The results obtained by giving anti-histaminics prophylactically to prevent vestibular damage suggested that some success was achieved but evidence was not conclusive.

ERIC COELHO.

STREPTOMYCIN IN POSTDYSENTERIC ARTHRITIS, Chaudhuri, R.N., Chakravarti, H., and Rai Chaudhuri, M.N.: Lancet 1: 510-511, 1951.

The authors treated a boy aged 15 years who was admitted with a history of pain and swelling of the left knee-joint and pyrexia after an attack of dysentery a fortnight before. The administration of salicylate, sulphadiazine and penicillin did not improve the joint condition. On the contrary the pain spread to other joints. Seven weeks after the onset of arthritis he was injected with Streptomycin 0.5 Gm. twice a day for a period of 21 days. The authors found the results striking as almost immediately after the beginning of the treatment, the pain in the left knee, right ankle and right shoulder began to subside and the temperature began to fall.

G. COELHO.

SIDE-EFFECTS OF CHLORAMPHENICOL AND AUREOMYCIN, WITH SPECIAL REFERENCE TO ORAL LESIONS, Tomaszewski, T.: B. M. J. 1: 388-391, 1 table, 32 references.

This summary has been based on observations of 126 cases treated with chloramphenicol and aureomycin in various wards of the Royal Infirmary of Edinburgh. In each case bacteriological examination showed that the pathogenic organ was sensitive to both the antibiotics. Both antibiotics were given orally in capsules of 250 mg., usually 2 capsules, sometimes more, were administered every 6 hours. Seventy patients (30 males and 40 females) received chloramphenicol, and 56 (32 males and 24 females) received aureomycin. The average dosage was 32 Gm. for chloramphenicol and 28 Gm. for aureomycin. The author reported that the gastro-intestinal symptoms occurred more often during treatment with aureomycin than with chloramphenicol. They were flatulence, nausea, vomiting, heartburn and diarrhoea. Rectal and genital changes were more common with aureomycin treatment and was especially marked in patients who had simultaneous oral lesions. The rectal changes consisted in redness, exudation, fissuring and in one case slight bleeding. In some instances the perineum was also red and tender. The patients usually complained of a burning sensation, itching, and sometimes actual pain. The genital changes comprised of vulvitis, with some fissuring and vaginitis accompanied by a slight discharge in women, whilst in men the genital symptoms were less frequent. Three complained of some scrotal and perineal itching and in one case, in whom oral changes were very marked, balanitis and a severe erythema of the scrotum and adjoining parts of the thigh and perineum developed a few days after chloramphenicol treatment. Oral manifestations were the most frequent structural changes encountered. The younger age group developed them more readily than the older ones. They were more frequent with aureomycin, and much more common in women than in men. Dryness of the mouth was observed in 39 per cent of the cases which resulted in hoarseness of the voice and actual sore throat. There was a noticeable diminution in salivation. The tongue changes were divided into two groups (*i*) atrophic glossitis, the more common type and (*ii*) hypertrophic glossitis with brown discoloration. These lesions of the tongue often affected the sense of taste in consequence of which appetite was often lost. Accompanying these tongue changes, redness of the mucous membrane of the mouth and throat with vesicular and papular changes were observed in some cases. In severe lingual and buccal lesions, angular stomatitis were often observed. The scrapings of the tongue generally showed a rapid disappearance of the normal bacterial flora and the establishment of a fungous flora usually composed of *C. albicans*. The author has discussed the danger of secondary mycotic invasion and stressed the similarity of oral changes produced by antibiotics to those found in vitamin B deficiency and has referred to the prophylactic and therapeutic effects of treatment with vitamin B complex.

ERIC COELHO.

A CLINICAL APPRAISAL OF NEOMYCIN, Waisbern, BA., and Spink, W. W.: Annals of Internal Medicine, 33: 1099-1119, 1950. 5 tables.

The authors have published a report of 63 patients treated with neomycin. This group comprised, 7 patients with tuberculosis, 17 with urinary tract infection, 3 with gram negative bacteraemia, 2 with staphylococcal infection, 7 with chronic respiratory infection and some with infections of unknown etiology. The usual dosage of neomycin was 0.5 Gm. four times a day but in some cases it was 0.5 Gm. twice a day as intramuscular injections. In 7 cases of tuberculosis, which included miliary tuberculosis, tuberculous meningitis and acute tuberculous empyema, no beneficial effect was noted though the drug was found to be well concentrated in the body fluids. Neomycin had a definitely beneficial effect on chronic urinary tract infections due to Proteus vulgaris and Pseudomonas aeruginosa. Out of 17 cases of the chronic urinary tract infection, 13 patients had their urine sterilized with neomycin. From the study of 11 patients with P. aeruginosa infection of the urinary tract, neomycin was found to be not so effective as against Proteus vulgaris. Four patients with E. coli infection of the urinary tract were successfully treated with neomycin; it was equally effective against A. aerogenes infection in eight patients. In all these cases no relation between the therapeutic activity and pH of urine was found. Two patients having P.vulgaris bacteraemia and one with A.aerogenes bacteraemia the response was good and the blood became sterile with neomycin therapy. Neomycin was equally effective in two patients with long standing staphylococcal sepsis, on 7 patients with chronic bronchitis and bronchiectasis and in two cases of peritonitis due to P.vulgaris. Three patients who were suffering from chronic sepsis, but in whom the aetiology of the disease was unknown, failed to respond to any other antibiotic but neomycin. Neomycin was well tolerated when given by mouth in doses of 2 Gm. every six hours. In no case was there observed any marked resistance to neomycin. Among the toxic effects it was found that the drug had an irritant effect on the kidney and 24 patients of 32 whose urine was examined, showed the presence of granular casts. The irritation of the kidney was only a transient phenomenon. In 5 cases neomycin had a direct toxic effect on the eighth nerve, but the auditory portion was affected before the vestibular, in contrast to streptomycin which attacks the vestibular function before the auditory one. This is unfortunate since the warning about the toxicity of neomycin is not received till a patient becomes " hard of hearing."

N. J. KOTHARI.

ACTH AND CORTISONE IN ACTIVE INFECTIONS, Editorial: Archives of Internal Medicine **87**: 1-3, 1951.

In the editorial of this issue a report of the effect of ACTH and Cortisone on active infections, has been given. Finland and his associates report that ACTH lowered the temperature in the patient with viral pneumonia but the physical signs remain unchanged. After treatment with ACTH for eighteen days, when it was discontinued, the temperature rose again and came down by lysis. The daily dose of ACTH given was 200 mg.; sodium retention, mild glycosuria and a rise in the eosinophil count with a rise in the total leucocyte count were observed during the treatment. In a patient with pneumococcic pneumonia, on administration of 150 mg. of ACTH daily, there was a drop in temperature to normal and also a clearing of the physical signs, but the sputum and the blood culture remained positive for type 8 pneumococci. Freeman and associates administered ACTH to two patients with active tuberculosis. There was a prompt fall in temperature, less coughing, a decrease in the amount of sputum, fall in E. S. R., and an increase in pulmonary translucence. The sputum was positive for tubercle bacilli at the end of the treatment. There was a definite spread of the tuberculous process in one patient and no improvement in the other. 70 patients with poliomyelitis were treated with ACTH, 40 to 120 mg. a day; there was no demonstrable effect in the treated as compared to the untreated. It is possible that more favourable results might have been achieved if the treatment had been started in the preparalytic stage. Animal experiments prove that with the administration of 50 mg. of Cortisone for four days, the mice developed septicaemia with group A haemolytic steptococci; in the control group no bacteraemia occurred. ACTH and Cortisone had no effect on mice and ferrets suffering from influenza. In rabbits, administration of ACTH and Cortisone inhibited sensitization to repeated intracutaneous injections of crystalline egg albumin; this was due to a suppression of the production of anti-bodies. It is recognised that lymphocyte activity is concerned with the manufacture and storage of antibodies; administration of ACTH or Cortisone results in a reduction of gamma globulin of the blood. It is likely that the suppression of antibody formation leads to a drop in temperature and increase in the sense of well-being while the activity of the pathogenic organisms goes on unchecked.

N. J. KOTHARI.

CLINICAL TRIALS OF A. C. T. H. IN HAEMOLYTIC ANAEMIA, Davidson, L. S. P., Duthie, J. J. R., Girdwood, R. H., and Sinclair, R. J. G.: B. M. J. **1**: 657-660, 1951.

The authors report the results of the administration of A. C. T.H. in three cases of haemolytic anaemia, 1 being acquired and the other 2 cases, congenital haemolytic anæmia In the case of acquired haemolytic anaemia, A.C.T.H. administered in a dose of 100 mg. daily for 10 days showed a rapid improvement in the haemolytic condition. A. C. T. H. administered in similar doses as above to the 2 cases of congenital haemolytic anaemia, gave little or no response in the haemolytic phenomena. The diagnosis of acquired haemolytic anaemia was evidenced by the negative family history, the positive Coombs test, the transient effect of blood transfusions, and the presence of abnormal antibodies in the serum. Despite the absence of a family history, congenital haemolytic anaemia was diagnosed by the clear evidence of haemolytic episodes in childhood, the presence of increased fragility of the erythrocytes in hypotonic saline, the absence of circulating agglutinins or haemolysins, and negative Coombs tests. The authors brought forward evidence to suggest that the control of haemolysis by A. C. T. H. in acquired haemolytic anaemia is not due to a suppression of the production of abnormal antibodies. Whether larger doses or a longer course of this hormone would have achieved more striking results can be determined only by further clinical trials.

ERIC COELHO.

THE RESPONSE OF MEGALOBLASTIC MACROCYTIC ANAEMIA TO CRYSTALLINE PENICILLIN G, a preliminary report, Foy, H., Kondi, A., and Hargreaves, A.: B. M. J. **1**: 380-383, 1951. 2 tables, 4 figures, 5 references.

The authors during the course of work on anaemias of Africans in Kenya observed an increase in reticulocytes, following the administration of crystalline penicillin G given for reasons other than anaemia. As these patients were given iron, marmite, or liver, the reticulocyte response could not be attributed to penicillin. They therefore decided to treat a case of macrocytic megaloblastic anaemia with nothing but penicillin. In this paper the authors report a case of megaloblastic anaemia where 400,000 units of crystalline penicillin G daily was administered for 7 days. The reticulocytes rose to 37 per cent and this was followed by a rise in the haemoglobin and red blood cells. The Price-Jones curve which had originally showed anisocytosis and macrocytosis reverted to the normal pattern. The megaloblasts had disappeared from the marrow by the fifth day of treatment and the giant stab-cells had become very much less numerous. The response that these authors obtained in no way differed from that obtained by giving potent liver extract, folic acid, Vitamin B_{12} or marmite. The writers suggest that the penicillin may have produced its effects by (1) destroying some organisms which were competing for haemopoietic substances; (2) removal of some haemopoietic antagonist; (3) preventing the absorption of glutamic acid competing organisms, which might thus interfere with the synthesis of pteroylglutamic acid; (4) affecting the metabolism and excretion of some essential amino-acids.

ERIC COELHO.

COLLOIDAL IRON: A WELL TOLERATED, EFFECTIVE, ORAL HAEMATINIC, Creakoff, A. J.: The Am. J. Med. Sc., 220: 553-558, 1950. 2 tables.

Various ferrous salts like ferrous carbonate, ferrous sulphate, iron and ammonium citrate, ferrous chloride, ferrous gluconate and reduced iron, have been used in the therapy of hypochromic, macrocytic anaemias but they have the disadvantage of producing gastro-intestinal irritation. One preparation which is effective as a therapeutic measure as well as being well tolerated, is colloidal iron, which is a preparation of iron combined with or dispersed in a colloid made by the digestive action of papain on casein. This preparation contains 20 per cent of iron and is stable and non-irritating. The author treated 25 cases of chronic hypochromic macrocytic anaemia with the administration of oral colloidal iron. The usual total daily dose was 1.2 Gm. divided into four 0.3 Gm. doses; a maintenance dose was prescribed after the gain of about 2.50 Gm. in the Hb. level. The average initial Hb. level of the group was 10.14 Gm. per 100 cc. of blood; in a period of 9 weeks the average gain was 1.56 Gm. per 100 cc. of blood. There was complete absence of symptoms of gastro-intestinal irritation. Another group of 23 patients mainly from the prenatal clinic, who showed heightened iritability and other abnormalities of gastric function, was chosen for the purpose of studies with colloidal iron. All experienced discomfort with ferrous gluconate and ferrous sulphate and had to discontinue the drug. This group of 23 patients experienced no irritation of the gastro-intestinal tract with colloidal iron. While the psychological factor is important in intolerance to iron, every effort was made on the part of the author to see that no pretreatment suggestion was conveyed to this group of patients.

N. J. KOTHARI.

CHEMOTHERAPY IN CHOLERA, Lahiri, S. C.: B. M. J. 1 : 500-504, 1951. 5 references, 7 tables.

In this study, the author observed the effects of sulphaguanidine, formosulphathiazole and formosulphacetamide in 268 patients. All these patients presented typical symptoms of cholera, with profuse rice-water stools, vomiting, and dehydration with anuria, prostration, and high specific gravity of blood. Powdered sulpha drugs mentioned above, were given orally to successive patients in cyclic order, the fourth one admitted receiving no chemotherapeutic drug, thus serving as a control. The dosage was the same for all the three compounds—4 Gm. initially, followed by 2 Gm. four hourly, for an adult, till the symptoms subsided or the stool became vibrio-free. Adjuvant treatment, such as saline transfusion, 5 or 25 per cent glucose, nikethamide, atropine sulphate, theophyllin and plasma, was given to all the patients when necessary. The author came to the conclusion that sulphaguanidine, formosulphathiazole, and formosulphacetamide when given orally did not reduce the mortality rate in cholera patients. These compounds had no special vibriocidal effect as the *V. cholerae* disappeared from the stools practically at the same rate both in the chemotherapeutic and control groups. The author observed that the adjuvant treatment played an important role in the treatment of cholera in that it quickly replaced the fluid and salt loss and prevented the development of circulatory collapse, subsequent anuria and complete renal failure. Hence chemotherapeutic drugs to be of real value in cholera, must have a quicker action than any of the sulphonamides tested in this study.

ERIC COELHO.

TYPES OF HUMAN DIABETES, Lawrence, R. D.: B. M. J. 1: 373-375, 1951.

The author has clinically divided human diabetes into two main types: (1) those who are probably not insulin-deficient, and (2) those who certainly are. The former type, the writer again divides into two, depending on the absence or excess of fat stores, using the terms lipoatrophic and lipoplethoric diabetes, respectively. The author cites a case each of lipoatrophic and lipoplethoric types of human diabetes and points out that in these two types there is a similar state of hyperglycaemia without ketosis but with opposite states of fat storage. He is of the opinion that these two types of diabetes are due not to insulin deficiency but to lack of an unknown hormone and/or enzyme system concerned with the regulation of the storage of fat. The insulin-deficient diabetes is of a severe type and present most difficult problems for the clinician both in its treatment and in the obscurity of its aetiological factors. In contrast to previous types, the characteristic feature is the ketosis which accompanies the hyperglycaemia and which, in the absence of insulin treatment, leads to coma. All diabetic children, and most adults under 40 and many over 70, are of this type, whereas lipoplethoric diabetes predominates between the ages of 45 and 60. They need insulin badly, and owe their lives to its continous use. The author in describing the different types of human diabetes and on speculating about their ætiological factors opens a field for further investigations along two lines, *viz.*, the histology of the islet cells and the insulin content of the pancreas and the estimation of blood insulin in various types.

ERIC COELHO.

SURGERY

THE REFRIGERATION TREATMENT OF CHRONIC OSTEOMYELITIS, Bringham; R.: California Medicine 74: 108-110, 1951.

The technique for the successful management of a case of chronic osteomyelitis can be divided into 5 phases, several of which are carried on simultaneously.

1. *Rest and immobilisation.*—The author feels that plaster casts are not necessary, but absolute bed rest, elevation of the infected extremity and immobilisation of the joints by splints during the active stage of infection are recommended.

2. *Chemotherapy.* Penicillin has supplanted other agents. The more slowly absorbing preparations are used in doses of 400,000 units twice a day and continued for 5 to 20 days from the beginning of treatment. For children under 12 the doses are decreased in proportion. If the organism can be cultured it should be tested for sensitivity to penicillin.

3. *Refrigeration.* The use of refrigeration to produce anaesthesia and to reduce the amount of septicaemia and infection and gangrene of the extremities is well known The rationale for its use is as follows:. Bacteria multiply rapidly at body temperatures or higher, but at greatly reduced rates at low temperatures. The human ex-

tremities can tolerate 57°F applied to the toes and fingers, 38°F applied to the calf and upper extremities and 32°F applied to the thigh. Thus the body tissues can be cooled to temperatures at which bacteria multiply slowly but the tissues are not injured. It also seems to enhance the effect of penicillin. Lesions thus become localised and virulence and toxicity of the infection is greatly lessened.

Refrigeration is begun as soon as the diagnosis of osteomyelitis can be made. A small lesion can be covered with one or two ice caps placed over a moist towel next to skin. A very acute or large lesion can be covered with one or two layers of moist towelling with crushed ice applied directly over the towel. This is kept constantly in place for from 5 to 14 days or until the evidence of local infection or inflammation has subsided. The ice is applied also after operations and refrigeration is continued until the wound appears to be healing well. The ice is removed once or twice during the day for an hour for observation of the character of the circulation in the limb and the extent of the infection. The temperature of the skin at the site of infection is always much higher than that of the skin in the surrounding area. If the skin over the lesion does not become warmer than that of the opposite normal limb when the pack has been removed for an hour, refrigeration is discontinued.

4. *Surgical drainage of abscess and removal of sequestrum.* In many cases the inflammation resolves under the above management and the limb returns to normal. In other cases an abscess will form and become localised and fluctuant. In that case all that is necessary is a short incision or a needle aspiration. Very often cultures of this fluid will be very sterile. A sequestrum if present is removed.

5. *Surgical obliteration of abscess cavity and primary closure.* When there is an intramedullary abscess cavity an open operation is necessary in order to drain the abscess and break down the sclerosed wall between the normal tissues and the centre of the abscess. This is done after a preliminary 24 to 48 hours period of penicillin therapy. At operation the periosteum is elevated and the cortex drilled until the central cavity is entered and pus exudes. The abscess cavity having been located, the roof of the cavity is removed by chiselling. The interior of the abscess is thoroughly curetted and irrigated with copious quantities of penicillin solution, 500 units per cc. With an electric bore drill multiple holes are made in the base both sides, and top and bottom of the abscess cavity until it resembles a sieve. In this way channels are opened up both for drainage and for invasion of granulation tissue from the adjacent normal tissue. The wound is again irrigated with penicillin solution and the soft tissues brought together; as much of the abscess cavity as possible is obliterated by turning the muscle and soft tissue during the closure. A padded dressing is applied. Refrigeration is continued for 5 days and penicillin for 7 to 10 days. At the end of this time the wound is usually healed and the temperature is normal.

E. J. BORGES.

PEDIATRICS

SODIUM SULFACETIMIDE FOR THE PROPHYLAXIS OF GONORRHEAL OPHTHALMIA NEONATORUM, Bickel, J. E.: J. Pediat; **37**: 854-857, 1950.

Credé in 1881 discovered that gonorrheal ophthalmia neonatorum could be prevented with the prophylactic instillation of 2 per cent silver nitrate solution into the conjunctival sacs of newborn infants. Since there are several disadvantages to this method, various substitutes have been recommended like 1 per cent silver acetate drops, sulfathiazole parenterally, penicillin as drops, penicillin intramuscularly, penicillin in combination with 1 per cent silver nitrate drops, and sulfacetimide.

The author reports a study with sodium sulfacetimide in an attempt to find a satisfactory substitute for silver nitrate for the prophylaxis of gonorrheal ophthalmia. The infants were divided into three groups. Group I comprised 682 patients who had 1 per cent silver nitrate drops; Group II, 642 patients who had 30 per cent sodium sulfacetimide drops; Group III, 583 patients who had 10 per cent sodium sulfacetimide ointment, making a total of 1,907 patients. Two cases of gonorrheal ophthalmia neonatorum developed, one each in Groups I and II.

Though further study is required, from this preliminary report the author has found sodium sulfacetimide especially the 30 per cent solution just as effective as 1 per cent silver nitrate in preventing gonorrheal ophthalmia. Besides producing less chemical conjunctivitis than 1 per cent silver nitrate, no severe allergic reactions occurred with sulfacetimide.

F. A. NAZARETH.

PRIMARY COMPLEX OF PULMONARY TUBERCULOSIS: Biggs, A. D., American Jour. Child. Dis., **80**: 566-574, 1950.

The author discusses the ordinary primary complex in infants and children, a lesion which it is generally agreed starts as inconspicuous parenchymal lesions which drain into the regional lymph nodes, and slowly harden.

The author's investigations indicate that none of the many minor disturbances to the child's health, such as fatigue, porlonged fever and cough, failure to gain weight, or mild anemia can be attributed to the ordinary or usual primary infection as has commonly been done. Some of them may be due to the massive primary complex which casts a large dense shadow on the roentgen film, a lesion which has in the past usually been referred to as epituberculosis.

The roentgen findings of the primary complex are inconspicious and not characteristic. A positive tuberculin skin reaction taken in conjunction with changing pulmonary shadows is diagnostic of the primary complex. Soft diffuse shadows which radiate from the hilus into the parenchyma but stop short of the chest wall are the earliest manifestations of the primary complex. These shadows which appear in one or more lobes do not make a simultaneous appearance. The upper lobes in the first and second intercostal spaces are the most common sites. Within a few weeks the hilar shadows become prominent; this hilar node involvement occurs so soon after parenchymal involvement, that seldom does one see a patient with peripheral shadows without hilar node enlargement. Though these nodular masses have well-defined margins, more frequently they appear as diffuse enlargements, or as a prominence of hilar shadows.

The peripheral shadows harden within two to three years, and end as inconspicious but definite linear shadows representing scar tissue. Deposits of calcium sufficient to be detected roentgenologically may take place in the parenchymal lesions forming Ghon tubercules. From the standpoint of roentgen examination, detection of the Ghon tubercle is the exception rather than the rule. It occured in 25% of 88 cases.

The hilar nodes also undergo the same healing process; hilar node calcification is however decidedly the rule in contrast to peripheral calcification which occurs infrequently. Hilar node calcification occured in 90 per cent of the author's cases. As a general rule, two years (minimum of six months to a maximum of five years) was the usual length of time for roentgen evidence of hilar node calcification.

The massive primary complex occured in 3 cases. These had various symptoms and signs which were mild in contrast to reontgen findings, which showed a conspicious shadow affecting a considerable portion of one lobe; these shadows persisted months after the symptoms had subsided. In each of these cases, tubercle bacilli were demonstrated by guinea-pig inoculation.

Children with the ordinary primary complex do not need any special treatment beyond removal from the source of infection; no isolation is necessary in these cases. Those with a massive primary infection should be treated with streptomycin; isolation is necessary as long as tubercle bacilli are recovered from the gastric washings.

F. A. NAZARETH.

TREATMENT OF DISSEMINATED HISTOPLASMOSIS WITH ETHYL VANILLATE, Christie, A., Middleton, J. G., Peterson, J. C. and McVickar, D. L.: Pediatrics, 7: 7-18, 1951.

Although a great majority of infections with *H. capsulatum* are benign or asymptomatic and clinically unrecognizable, the hopeless outcome in the progressive type of infection has prompted treatment with several agents which have all been uniformly ineffective. The authors' report their experiences with the use of ethyl vanillate in 12 cases of culturally proved histoplasmosis of the progressive disseminated type.

Ethyl vanillate (ethyl 4-hydroxy-3-methoxy benzoate) is a by-product of the sulphite pulp manufacturing process. It is obtained as a solid having a slightly phenolic odor and a strong cinnamon-like taste. It is soluble in organic solvents, and has reactions characteristic of a phenol and an aromatic nucleus. It has been shown to inhibit growth of *H. capsulatum* in concentrations of 20 mg./100 c.c. A narrow margin exists between therapeutic levels and toxic manifestations, making adequate laboratory controls imperative.

The drug causes a burning sensation to the mucous membranes of the mouth, and in infants has to be given by gavage as a 40 per cent. solution in olive oil; the use of a small indwelling polyethylene tube having an advantage over repeated intubations. To avoid possible gastric irritation, it was found necessary to give the oily solution with the feedings. The authors' suggest that the initial dosage in infants without diarrhœa be 0.5 Gm./Kg./day in divided doses, and that this be increased in steps of 0.5 Gm. every 5 to 6 days until a dosage of 1.5 Gm./Kg. /day or a blood level of 20 to 30 mg. /100 c.c. be attained. Levels higher than these have been associated with toxic manifestations. In adults, smaller doses are required, less than 50 per cent. of the dose as calculated on a weight basis. When severe diarrhœa is present, larger amounts are required. As therapeutic levels are not maintained for longer than 5 to 6 hours, the drug has to be given in 4 to 6 daily doses. Although the time needed for treatment is not clear, the authors' have maintained therapeutic levels for a minimum of 42 days realizing that the infection was a chronic granulomatous process.

Toxic manifestations have been observed; all the infants showed slight drowsiness, apathy, and inactivity which passed off when the drug was stopped, three patients developed sudamenal rashes, one had drug fever. Hyperpnoea has been noticed at some time in several infants; moderately high doses in two cases resulted in respiratory alkalosis. In one fatal case with a toxic blood level (56 mg./100 c.c.) autopsy revealed necrosis of the hepatic cells round the central veins, and degenerative changes in the proximal convoluted tubules.

Of the 12 cases studied, 5 have survived and are still well, the authors' believe that they have survived because of treatment. The results are encouraging because most of the failures were either too ill, or associated with factors which otherwise precluded adequate treatment. Case reports of all the surviving patients and two of the non-survivors are given in some detail.

F. A. NAZARETH.

OBSTETRICS

TREATMENT OF THREATENED ABORTION, Stallworthy, J.: The Pract. **166**: 118-123, 1951.

The usual sign of a threatened abortion is slight painless bleeding during the first twelve weeks of pregnancy. Pain is not usually a feature of threatened abortion, but in some cases is the only symptom. Its site is characteristically in the midline of the hypogastrium and it may be of a dull aching type or intermittently colicky. The fundamental principle in the treatment of threatened abortion is to prevent it from becoming inevitable. The importance of prophylaxis should not be forgotten. Avoidance of fatigue and motion of long journeys by car, intercourses, excessive purgation and gross constipation should be emphasised. At the first warning of haemorrhage or pain, absolute physical and mental rest should be advised. Mental rest is promoted by the action of sedatives like morphine gr. ¼, medinal grs. 10 by mouth or phenobarbitone grs. 3 by intramuscular injection. If pain is more a feature than haemorrhage, the aim of treatment is to promote uterine relaxation by giving glycerly trinitrate, gr. 1/100 by mouth, four-hourly if necessary or it may be combined with phenobarbitone grs. 2 or 3 by mouth. Vaginal manipulation should be avoided. The less done to the body of the uterus during the stage of a threatened abortion the better for the safety of the ovum. The use of hormones in threatened abortion is still controversial but at the present time the weight of clinical evidence is in favour of this procedure. An initial dose of 20 mg. of progesterone or a comparable product like progestin, proluton, lutocyclin, gestone, luteostab, lutren, given intramuscularly followed by 10 mg. daily till the patient is active again, should be adequate. The patient should be at complete rest till a week after the cessation of the phase of bright bleeding. The presence of a brown discharge is of no serious significance, it is due to the liquefaction of the intra-uterine clot at the site of haemorrhage. Whenever abortion has threatened, many patients are fearful lest the foetus be damaged in case the pregnancy continues. They should be reasured that nothing will happen. The time taken to explain to the patient what is happening and to reassure her, is time well spent.

ERIC COELHO.

SKIN

THE TREATMENT OF IMPETIGO, Fox, P. B: The Pract. **166**: 189-192, 1951.

Impetigo contagiosa is an infective condition of the skin, probably caused by the staphylococcus or streptococcus and occurring mostly in children, affecting the exposed areas—face, neck, ears, and hands, although no area of the body is immune.

Differential Diagnosis. The essential lesion is a vesicle or bulla, the serous contents of which quickly coagulate to form the characteristic golden crusts with that peculiar 'stuck on' appearance. Impetigo must be distinguished from secondarily infected scabies and papular urticaria, in that, the latter condition affects mostly the trunk and limbs which is unusual in primary impetigo. When affecting the scalp, the back of the neck, and even the face, impetigo calls for careful investigation to exclude pediculosis capitis. Occasionally tinea capitis simulates impetigo, but broken hairs usually provide the clue; sometimes microscopic examination may be needed. Herpes simplex lesions must be carefully examined. They usually appear in a group or groups of small vesicles on an inflamed base. If the impetigo keeps recurring at exactly the same site it is almost certainly herpes. Less often herpes zoster of the trigeminal and cervical nerves causes difficulty. The unilateral zonal distribution of the grouped vesicles, associated with the rather characteristic pain, usually suggests the diagnosis. Seborrhoeic dermatitis should be differentiated from impetigo too. This dermatitis is characterised by a chronic recurring, weeping, crusted, eczematous condition affecting the scalp and eyebrows, with symmetrical involvement of the face, ears and retro-auricular areas. Blepharitis is constantly associated with this condition.

Treatment. In general, the treatment consists in gentle cleansing and the use of mild astringent and antiseptic applications. The cleansing of the affected areas is important in the inital stages. For the scalp, shampoos may be used freely. On the body, potassium permanganate, 1 : 4000 or boric acid solution or even soap and water may be used. When the condition is widespread, baths using the same medicaments, are very helpful. In a localised area of rather adherent crusts and debris, starch poultices or saline compresses are particularly effective. Following the use of any of the above cleansing procedures, mild antiseptic and astringent lotions are used. The lotions of choice are Dalibour water (Lotio cupro-sincica, N. F.), mercuric chloride lotion, 1 : 1000, lead lotion, silver nitrate solution, 0.5 to 1 per cent., and proflavine lotion, 1 : 2000. To the last-mentioned may be added tannic acid, 2 to 5 per cent which enhances its efficiency considerably. These lotions should be applied liberally every two or three hours until the exudation has ceased, when they may be used less often or substituted by ointments or pastes. When once the condition is relatively dry, pastes and ointments are satisfactory vehicles. Lassar's paste with 2 per cent ammoniated mercury is one of the best preparations for this condition. Yellow oxide of mercury, 2 to 3 per cent., sulphur, 2 to 5 per cent., and gentian violet, 0.5 to 2 per cent, are also useful alternative medicaments that may be incorporated. These pastes and ointment should be applied twice a day, preferably spread on to thin calico dressing rather than directly on to the skin. The following day the debris may be cleansed with medicaments mentioned above. The oxyquinoline ointments, 'quinolor compound ointment' (Squibb) and 'vioform ointment' (Ciba) are useful preparations in the dry type of impetigo but it is unwise to use them in the acute inflammatory stage, and it is always best to use them at first half-strength mixed with equal quantitites of emulsifying ointment (B.P.) Lassar's paste, or zinc cream (B.P.C.). This precaution avoids undue reactions, and the patient's tolerance can then be assessed. In the dry mild types of impetigo, all that may be necessary is lotio calamine with mercuric chloride, 1/8 grain to the ounce, ichthyol, 3 to 5 per cent.; gentian violet, 1 to 3 per cent.; or sulphur, 2 to 5 per cent. Calamine lotion should not be used in the exudative stage because of the undesirable caking of the exudate and deposited zinc powders.

Impetigo of the scalp and beard. The difficulties encountered in these conditions is due to the hair. In the scalp shampoos may be used freely in the initial stages to remove exudate and medicaments, and prevent matting of the hair. The shampoos suitable for the purpose are alcoholic solutions of green soap or one of the newer sulphonated oils. If the hair is short, both lotions and ointments are satisfactory applications. Mercuric chloride lotion, or proflavine lotion 1: 2000, may be applied twice or thrice a day. Emulsifying ointment (B.P.), with yellow mercuric oxide, 2 to 4 per cent., gentian violet 0.5 to 1 per cent., are preferable. When the hair is long, cutting is rarely necessary, and in women it should be avoided at all costs. The above lotions may be used, and the thin creamy emulsion, hydrous emulsifying ointment, with mercurials incorporated is an excellent preparation. Impetigo of the beard presents a difficult problem. It is best not to shave. The hair should be clipped short by means of sharp scissors. The usual lotions may be used throughout the day and at night, zinc cream (B.P.C.), or hydrous emulsifying ointment (B.P.) with yellow oxide of mercury should be applied. When the condition is rather stubborn, the following application may solve the problem : Zinc cream (B.P.C.); oily calamine lotion, hydrous emulsifying ointment (B.P.) with gentian violet 0.5 to 1 per cent; paint of brilliant green and crystal violet, 8 Gm. to 28 cc. or argyrol 0.12 to 0.25 per cent. Full dosage of sulphonamides and injections of penicillin 100,000 units twice a day are useful adjuvants to topical therapy.

Complications of Treatment. The most frequent complication is an acute dermatitis as the result of the topical applications used. The type of base used in the source of this trouble. In acute exudative conditions, avoid greasy ointments. Sometimes the skin acquires a definite allergic hypersensitivity to some element in the base. Often the medicaments incorporated act as primary irritants especially when used in too high a concentration. The use of mercury in combination with sulphur or iodine not infrequently bring about reactions and therefore the use of these medicaments together should be avoided. Penicillin and sulphonamides should be used as topical applications for not more than a week as these medicaments sensitize the skin and their use after that proves hazardous. Penicillin in aequeous or saline solutions, 500 to 1000 units per cc. does not sensitize the skin.

ERIC COELHO.

MULTIPLE SIMULTANEOUS ANOMALIES OF THE HAIR : Morris Zeider, Arc. of Derm & Syphilology : 62 : 510-514 : 1950.

The author reports a case of a female aged 39 years who complained of brittleness of scalp hair. She had three such episodes; the first at the age of 9 in conjunction with an attack of influenza, the second at the age of 22 following a long illness due to pleurisy and the third is the present one followed by twin pregnancy. Her previous child, a girl, had ringed hairs.

An examination of scalp hairs, the author found them of 3 varieties. (1) Pili annulati or ringed hairs (2) Trichorrhexis nodosa and (3) Trichostasis spinulosa.

While commenting on these anomalies found in the same case, the author feels that they are not so rare as made out in general textbooks in dermatology. Only vigilance and diligence are required to detect them.

Trichostasis spinulosa is quite common if sought for. It is a condition in which bundles of hair containing a number of laringo filaments are surrounded and enmeshed in a sheath of amorphous debris. It appears as a comedo-life structure plugging the pilosebaceous orifices of nose or eye brow.

The occurrence of piliamulati in the mother and the daughter in this case suggests that it is a gene-determined anomaly. Regarding trichorrhexis nodosa the author suggests that it is the result of a metabolic disturbance as observed in his case and many others. Dilating further he says that one may imagine that under circumstances of considerable physical depletion, such as may occur in influenza, pleurisy and twinning, less important structures of the body, *e.g* , hair and nails may be deprived of their normal quota of nutrition, perhaps a case of "survival of the fittest."

Trichorrhexis nodosa is a condition of hair in which brush fractures occur a various points on the hair length. Microscopic observation suggests that the potentiality to fracture is present all along the shafts of such metabolically disturbed hairs. Then such factors as trauma due to washing, combing and movements of the head on pillows determine at what lengths, where and how often hairs are broken off. Under the circumstances the most valuable treatment will be mechanical protection of hair from injury of all sorts until the underlying metabolic causes abate or disappear. Identical condition occurs in animals. Treatment of the case consisted of (1) mechanical protection of the hair by avoiding combing, washing and putting a cap at night (2) salicylic, acid, mercury or sulfur and resorcinol lotions and ointments (3) thyroid by mouth and (4) ultraviolet irradiation. The patient recovered after nine months.

T. K. MEHTA.

ANTIHISTAMINICS IN DERMATOLOGY, Lewis, G. M.: Med. Clin. N. Amer. 333-340, 1951. 1 table, 1 figure, 3 references.

The antihistaminic drugs are useful adjuncts to the therapy of many pruritic cutaneous diseases. The explanations advanced to explain the action of antihistamines are that they may (*a*) prevent release of histamine, (*b*) neutralise histamine after it is formed; (*c*) compete with histamine for chemical combination with the cell; (*d*) stimulate the sympathetic system and thus oppose the action of histamine; (*e*) in the case of their local use, a procaine-like effect is apparently induced. Most of the antihistaminics require a dosage of at least 25 mg. thrice daily, after meals, to be effective. This dose can be used when thephorin, trimeton, decapryn, tagathen, histadyl, or thenylene are prescribed. Benadryl and pyribenzamine may be given in 50 mg. doses. Particularly in children, liquid preparations are advantageous, the elixir of thephorin and of benadryl both containing 10 mg. of the drug per teaspoonful. In acute cases, the antihistaminic drugs are given parenterally, the solutions of benadryl and histadyl containing 10 mg. per c.c. It has been observed that a combination of two or more of these drugs sometimes proves beneficial. In general the antihistaminics are well tolerated by babies and children. The chief value is to be found in the group of psychosomatic disorders including anogenital pruritus, essential pruritis in other areas, atopic eczema (neurodermatitis), and urticaria. The relief from pruritis is often dramatic although invariable.

ERIC COELHO.

NOTICE TO SUBSCRIBERS

Subscription Rate: Price per annum (including postage) *payable in advance:* Indian, Rs. 10; Foreign, Rs. 15. Single copy: Re. 1 postpaid.

Remittances: Should be made by cheque, draft, postal order, and money orders. All cheques, etc., should be crossed and made payable to "Indian Journal of Medical Sciences".

Change of Address: Notice of Change of Address should be received at least one month prior to the date the change is to go into effect, and should state whether the change is permanent or temporary. Both old and new addresses should be given.

All communications regarding subscriptions, change of address, etc., should be addressed *quoting the Subscription Number* to the "Indian Journal of Medical Sciences," Back Bay View; Opp. Charni Road Gardens, New Queen's Road, Bombay 4.

NOTICE TO ADVERTISERS

All advertising copies, pulls, mats, stereos, etc. (intended for any particular monthly issue) must reach the Office of the " Indian Journal of Medical Science ", Back Bay View, Opp. Charni Road Gardens, New Queen's Road, Bombay 4, by the *first day of* the month *preceding, e.g.*, those for the December, 1947, issue must reach us by the first day of November, 1947.

Unless this is strictly followed, the publishers cannot guarantee insertion of advertisements in any particular issue or issues.

No additions, alterations or omissions to the advertising copy, pull or stereo, etc., can be entertained after the *seventh day of the month preceding*. Changes in the " copy " or lay-out when accepted by the Press, are charged at cost.

Unless distinctly instructed to the contrary the same advertisement of an advertiser will be repeated from month to month till the contract is over.

No advertisement will be accepted unless the composition of the preparations to be advertised is given.

Indian Journal of Medical Sciences
(INCORPORATING THE MEDICAL BULLETIN)

VOLUME 5 JULY 1951 NUMBER 7

COPYRIGHT BY THE INDIAN JOURNAL OF MEDICAL SCIENCES

CARCINOMA OF THE CERVIX

A Review of 525 *cases diagnosed by Biopsy*

E. W. Gault, M. Asirvadham, M. Balasubrahmanyan, G. W. L. D'Sena, E. Thomas and P. Isaiah *

INTRODUCTION

Carcinoma of the uterus is considered by Willis[35] to be one of the three commonest causes of death from cancer in women and that carcinoma of the cervix is much more frequent than carcinoma of the body of the uterus. In recent years there have been a number of reviews of cases in the endeavour to analyse the types, symptoms, treatment and possible etiological factors. Sadugor and Palmer[31] analysed 4,652 cases over the period 1917-1947. Pollack and Taylor[28] reviewing the literature found 30 cases occurring before the age of 20. Maliphant[22] analysed 1,200 cases and discussed the relation of childbirth and chronic cervicitis to the incidence of malignancy. Given[15] reported 212 cases over the period 1933-44 and discussed the relation to childbirth, symptoms and histological and clinical types. DeAlvarez[9] reported on 55 autopsies while Henrikson[18] analysed 420 autopsies. Brunschwig[7] reported 65 autopsies and analysed the factors resulting in death. Meigs, Parsons and Nathanson[23] reported a series of cases occurring after supravaginal hysterectomy. Borges[5] has recently analysed a series of cases treated in Bombay.

This review was undertaken because of the high incidence of carcinoma of the cervix in Vellore. In the course of this study 10 cases of carcinoma of the corpus uteri, 14 of chorionepithelioma and 7 of tuberculosis of the cervix were encountered. Carcinoma *in situ* is not dealt with in this paper as the method of taking the biopsies in the past has not revealed this. The cervical cone knife described by Ayre[3] is now being used in this hospital and the results of this investigation will form the basis for a future enquiry.

---

* Department of Pathology, Christian Medical College Hospital, Vellore, S. India.

MATERIAL AND METHODS

The material was received from the gynæcological clinic and the task of reviewing the biopsies taken from the cervix uteri and analysing the material in the hospital records has been shared among the authors. We have reviewed the great majority of the slides, together in conference and have rejected all cases in which a histological diagnosis has not been established even though the clinical signs and symptoms or vaginal smears suggested malignancy. The grading of the cases and the opinions expressed are those of the joint authors. No discussion of the cytodiagnosis of carcinoma of the cervix is made in this paper as it forms the basis of another paper by Balasubrahmanyan[6]. There were no opportunities for follow up and hence there is no attempt to evaluate the therapeutic results.

AGE INCIDENCE

The age incidence of carcinoma of the cervix as met with in this series is presented in Table 1. The age was recorded only in 400 of the 525 cases. The youngest patient was aged 19 years and the oldest 78 years.

TABLE 1.—*Age Incidence.*

Years.	No. of Cases.	Years.	No. of Cases.
Below 20	1	50—54	49
20—24	5	55—59	29
25—29	20	60—64	8
30—34	49	65—69	1
35—39	85	70—74	1
40—44	86	75—80	1
45—49	65		

Youngest 19 years. Oldest 78 years.

Compared with Willis' figures the percentages show the higher percentage in the younger age groups and the lower percentage in the older age groups may have some relation to early marriage, pregnancy and the lower average expectation of life in India.

TABLE 1a.—*Percentage Age Incidence of Carcinoma of the Cervix (Willis)*

Age in Years	Under 30	30	35	40	45	50	55	60	65	Over 70
Willis	4%	9%	16%	20.0%	19%	15%	9%	5%	2%	1%
Vellore	6.5%	12%	21%	21.5%	16%	12%	7%	2%	0.5%	0.25%

Ewing[12] considers that carcinoma of the cervix occurs most commonly in the 5th decade and Salvatore DiPalma[11] states that half the cases occur between 40 and 55 years while Sadugor[31] records the peak age incidence as 47 years. In this series over half the cases occurred between the ages of 30 and 44 which emphasises the lower age incidence in South India. Salvatore DiPalma[11] records two cases aged 20 years while Given[15] in a series of 212 cases states that the youngest patient was 24. Pollack[28] reports one case aged 18. Borges[5] reporting on 106 consecutive cases occurring at the Tata Memorial Hospital, Bombay, records the maximum incidence between 30 and 49 years. The youngest case being 22 years and the oldest 70 years.

MARITAL STATUS

In this series there was only one unmarried patient who was an European. As it is uncommon to find spinsters in India, no conclusions can be drawn regarding the relation of marriage to carcinoma cervix.

NUMBER OF PREGNANCIES

Table 2 shows the number of pregnancies in the 261 cases where this was recorded. One patient had primary amenorrhœa and had never menstruated. There were nine nulliparous women. One patient had fourteen pregnancies. The number of cases of carcinoma of the cervix in patients with 3, 4, 5 and 6 pregnancies do not show much variation. As large families are the rule rather than the exception in India no conclusions can be drawn from these figures but it is of interest to note that 1.75 per cent of the recorded 234 cases had never been pregnant. Willis[35] makes the comment that the number of pregnancies has no relationship to the incidence of carcinoma of the cervix. Gusserow, Koblanck and Williams (quoted by Ewing) state that the childbirths average 5.

TABLE 2.—*The Number of Pregnancies.*

No. of Preg.	No. of Pat.	No. of Preg.	No. of Pat.	No. of Preg.	No. of Pat.
0	9	5	34	10	7
1	28	6	35	11	4
2	24	7	19	12	4
3	40	8	16	13	2
4	29	9	7	14	1

INTERVAL FROM LAST CHILD BIRTH

The analysis of 133 cases where this was recorded in the histories, is shown in Table 3. It is interesting to note that in 73 per

TABLE 3.—*Duration Between Last Child-birth and First Examination in* 133 *Cases.*

Period in years	No. of Cases.	Period in Years.	No. of Cases.
0	6	10	24
1	13	15	19
2	9	20	3
3	8	25	1
5	49	30	1

cent of these, the patients came for treatment five years or more after the birth of the last child. The longest interval was 35 years. The theory that the raised œstrogen content of the blood during pregnancy should be an important factor in producing carcinoma of the cervix is not very likely to be true in view of the fact that 97, or 73 per cent of this series came for treatment 5 years or more after the birth of the last child, and 48 cases, or 36 per cent came for treatment after 10 years or more.

CARCINOMA OCCURRING DURING PREGNANCY

This was found in 8 cases (1.5 per cent) and in one case a Cæsarian section was performed. Sadugor and Reinhard[32] in reviewing 4652 cases of carcinoma of the cervix found that 2.6 per cent were pregnant or had been pregnant within a year before admission. He considered that they had an identical cure rate as compared with non pregnant cases although Ewing[12] states that pregnant cases run an unfavourable course. We were unable to follow up our cases.

Lapan[26] raises a note of warning when he points out the danger of mistaking a hard nodule in the cervix with decidual changes, for malignancy.

PROCIDENTIA

Two cases occurred in patients suffering from prolapse. Willis[35] has pointed out the rarity of this coincidence as an argument against any traumatic theory of the origin of carcinoma of the cervix. A careful examination of the cervix in all cases of hysterectomy for procidentia might reveal more cases in early stages even when the portio cervicalis appeared intact.

SUPRAVAGINAL HYSTERECTOMY

One case was met with in the cervical stump, in which a subtotal hysterectomy was done for uterine fibromyoma. A cervical polyp removed 19 years later was found to be malignant and histological section showed a transitional celled epidermoid carcinoma. Crosbie[8] has recorded between 1929 and 1944, 62 such cases, 9 of which were multipara.

Given [15] stresses the importance of examining the cervix carefully before subtotal hysterectomy.

RELIGION

Twenty-one cases (4 per cent) occurred among Muslims and 17 cases (3 percent) among Christians. It has been suggested that the disease is rare among Muslims although Willis quotes Nath and Grewal[25] as stating that in 1830 cases of cancer among Hindu women, 48 per cent were of the genital tract and in 666 cases in Muslim women, 33 per cent were genital. Remembering the purdah restrictions which often prevent Muslim women from coming for treatment the percentage difference is not significant. The percentage of Muslim women attending the gynæcological department of this hospital for all diseases from July 1945 to October 1950 was 6.3 per cent. Muslim women therefore do not seem to enjoy any special immunity. At one time the Jewish community was also thought to enjoy a similar immunity but Salvatore DiPalma[11] reports 4.2 per cent of cases from the Memorial Hospital, New York, as occuring in Jews. Borges[5] considers that the proportion of Muslims treated at the Tata Memorial Hospital is lower than would be expected.

SYMPTOMS

It was extremely difficult to evaluate these, as available data were inadequate and often misleading. In half of the cases there was a record of bleeding per vaginum and leucorrhœa while in 33 per cent of the cases there was lower abdominal pain which in 12.5 per cent of the cases radiated down the legs. In only 13 (2%) was there a history of bleeding after coitus but the essential reserve of Indian women may have been responsible for the failure to elicit this symptom.

The analysis of the 123 cases of which records are available may be shown in tabular form (Table 4).

TABLE 4.—*Time Interval Between Onset of First Symptom and Examination.*

History	Cases.	
	Number.	Percent.
Less than three months	26	21.1
,, ,, six months ..	35	28.5
,, ,, one year	40	32.5
,, ,, two years	17	13.8
,, ,, three years	1	0.8
,, ,, five years	3	2.4
Eight years	1	0.8

Pohle[27] quotes Clarke and Ferguson who state that 60 per cent of patients who applied for treatment within 6 months of the appearance of their first symptoms were found to have advanced carcinoma. The duration of the symptoms bears little or no relation to the extent of the carcinoma. He considers that pain occurs when the parametrium or bony pelvis is invaded. Menopause had occurred in 85 patients and Table 5 shows the relation of the onset of menopause to the time when the patient came for treatment. It is significant that nearly 50 per cent of the cases presented for treatment five years after the onset of menopause. If circulating œstrogens are of importance their action must persist for a long time.

TABLE 5.—*Duration of Menopause.* (85 Cases)

Years	No. of Cases
0	9
1	11
2	6
3	10
4	7
5	25
10	7
15	8
20	1
25	1

CLINICAL STAGE

An attempt has been made to classify the cases according to the League of Nations Grouping, as described by Pohle[27]. The majority of the cases presented with very advanced lesions, so that comments such as "frozen pelvis" or "vagina completely filled with growth" were common in the records. 7 per cent of the cases were in stage I or II. 47.6 per cent in stage III or IV. While in 45.4 per cent data were inadequate to make a classification. A vesico-vaginal fistula was present in 4 cases. This is in marked contrast to the American figures given by Given[15]. He records 7 cases of fistulæ in a series of 212 patients with 65 per cent in stage I or II and 35 per cent in stage III or IV. Lock and Caldwell[20] state that in 1943, 33 per cent of their cases were in stage I or II while in 1946-48 there were 70 per cent in this group. This stresses the importance of a campaign for early diagnosis. Arenson[1] refers to three main types based on the gross macroscopic appearance of the cervix; (1) Everting cauliflower-like, (2) infiltrating and (3) cratering or ulcerating. In the cases seen in this series the majority belonged to the first type, a few to the third, while the second group was the least common. Examples of these three types are seen in the illustrations

(Fig. 1, 2, 3 and 4). The ulcerating type is responsible for fistula formation, as is also the infiltrating. A good example of the infiltrating type with extension up into the corpus uteri is seen in Fig. 2. In this case there was no gross evidence of a tumour on the portio cervicalis although the tumour itself was the transitional type of epithelioid carcinoma while adenocarcinoma is commoner in this situation. Henrickson[18] points out that 25 per cent of the cases classified according to the League of Nations system were proved to be incorrect at autopsy. This was due to the inflammation of the parametrium being mistaken for malignant infiltration. Similarly enlarged glands may be inflammatory and not infiltrated with malignant tissue. All workers are agreed that the infiltrating type is much more malignant than the fungating cauliflower type. Most of our cases were so advanced that it was impossible to identify the cervical canal which Kaufmann[19] states remains unaffected for a considerable time in the fungating variety arising from the portio cervicalis. There were several examples of pyometria from blockage of the canal. The malignant infiltration of the lymphatics extends outwards into the parametrium and along the course of the uterine artery. Where this crosses the ureters, there is not infrequently a stenosis causing hydroureter and hydronephrosis above. This is well seen in Fig. 5 from an autopsy specimen. Willis[35] refers to the adherence of coils of intestine to an area of pelvic peritonitis leading to intestinal obstruction. This was noticed in one of our cases at autopsy.

HISTOLOGY

Carcinoma of the cervix may be epidermoid in the type arising from the portio cervicalis or largely but not solely adenocarcinoma, arising from the endocervix or body of the cervix. All authors agree that the epidermoid form is much commoner than adenocarcinoma. Willis[35] states that it occurs ten times more frequently than the latter. Salvatore DiPalma[11] gives the incidence of adenocarcinoma as 3.2 per cent while Given[15] gives a figure of 7.9 per cent—five of the cases being first diagnosed as adenocarcinoma of the fundus and subsequently shown to have arisen in the cervix. Morehead[24] points out that under the age of 20 years the majority are adenocarcinomata. Sadugor and Palmer[31] point out that the adenocarcinomata occur on an average five years later than the squamous celled type. In our series adenocarcinoma formed only 1.3 per cent.

Martzoff, of New York divided the epidermoid type into three groups :—

1. *Spinal.*—with large cells and big deep staining nuclei which resemble the cells of the superficial layers of the stratified squamous epithelium. They may or may not show prickles.

2. *Transitional.*—an intermediate type.
3. *Spindle.*—closely packed cells with little cytoplasm between the nuclei which are spindle in shape and resemble the cells of the basal layer.

These three groups correspond to grades 1, 2 and 3 of Broders classification. An analysis of our material based on careful review of the sections is represented in Table 6.

TABLE 6.—*Histological Types of Malignancy.*

Type	%
Spinal	7.0
Transitional	65.0
Spindle	5.0
Mixed	17.0
Adenoacanthoma ..	0.2
Adenocarcinoma ..	1.3
Unclassified	4.0

Spinal (7%) and Spindle celled (5%) types in pure forms are relatively uncommon. Transitional celled type (65%) forms the largest group. Pure examples of these three groups are seen in Fig. 6, 7, and 8. The history in these cases varied from a well differentiated keratinized form of epithelioma (Fig. 9) to an undifferentiated sarcoma like picture (Fig. 10). The transitional celled group proved to be a very unwidely one which contained many varieties. A small celled type is seen in Fig. 11. The frequent occurrence of the three types in the same tissue (17.5% of our cases) and the small proportion of pure spinal and spindle forms throws doubt on the real value of this form of classification. Willis[35] states categorically that the cytological diversity renders any attempt at precise grading, arbitrary and futile. Given[15] states that there is no correlation between histological grading and survival rate. Borges[5] finds difficulty in assessing the prognosis from the cell type. Adenoacanthoma was present only in one case (Fig. 12). Four per cent of the cases could not be satisfactorily classified.

The arrangement of the cells varied greatly. In some cases there were simple sheets of cells with very little stroma while in other cases there were infiltrating columns of epithelial cells (so aptly described by Ewing[12]) which could be clearly seen while in others the cells were arranged in islands with club-like processes closely resembling the picture seen in basal celled carcinomata (Fig. 14). In one section there was calcification in the centre of the epithelial pearls (Fig. 15) and in another cell nest formation was seen occurring in a transitional celled tumour (Fig. 16). In several sections the arrangement of narrow cords of cells in a dense fibrous stroma closely resembles that seen in a scirrhus

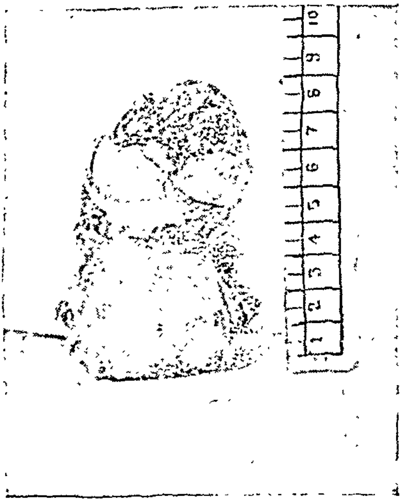


Fig. 1. Macroscopic appearance of fungating carcinoma of cervix.

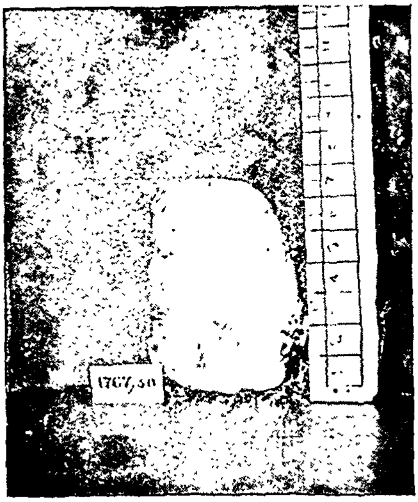


Fig. 2. Macroscopic view of infiltrating carcinoma of cervix.

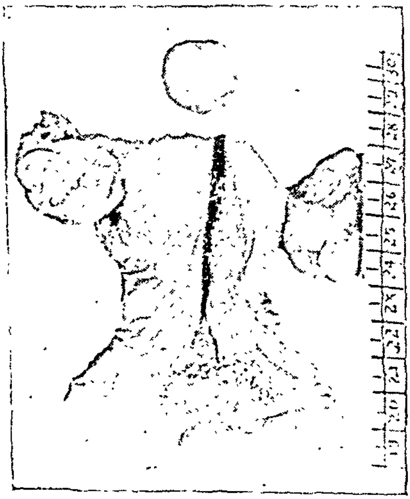


Fig. 3. Macroscopic appearance of an ulcerating carcinoma of cervix. The infiltrated pre-aortic gland is seen above the fundus of the uterus.

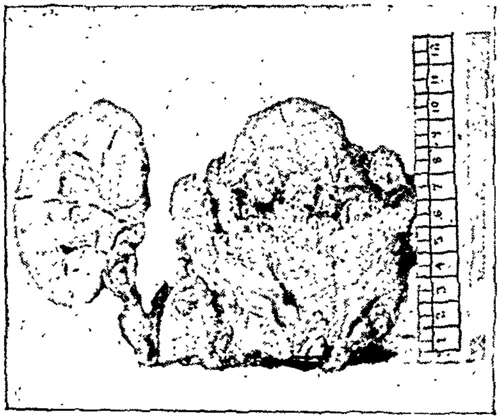


Fig. 4. Macroscopic appearance of an ulcerating carcinoma of the cervix infiltrating the lower end of the ureter leading to Hydronephrosis.

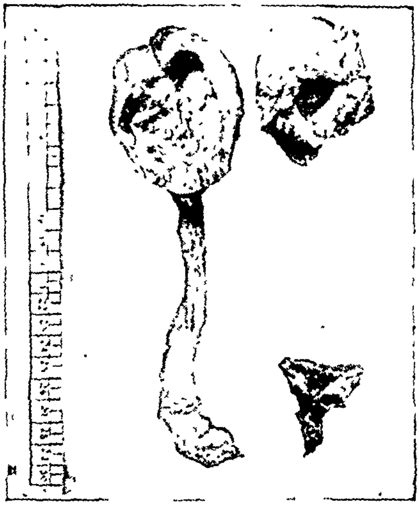


Fig. 5. Macroscopic appearance of infiltration of the lower end of the ureter which is so thin that the photograph does not show it resulting in Hydroureter and Hydronephrosis.

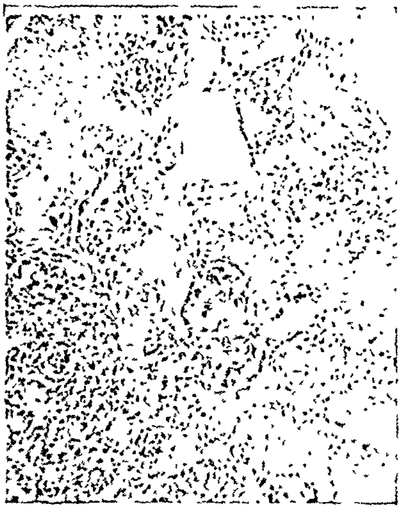


Fig 6. Photomicrograph—spinal celled type of epidermoid carcinoma × 110.

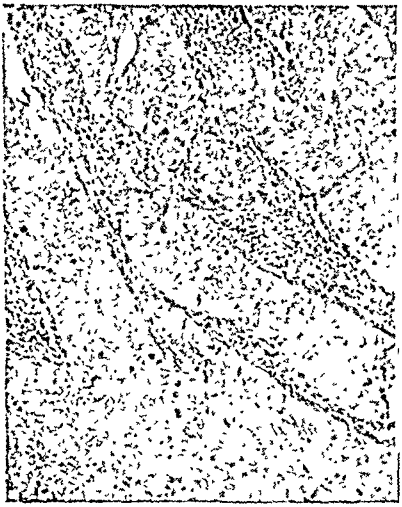


Fig. 7. Photomicrograph—Transitional celled type of epidermoid carcinoma × 110.

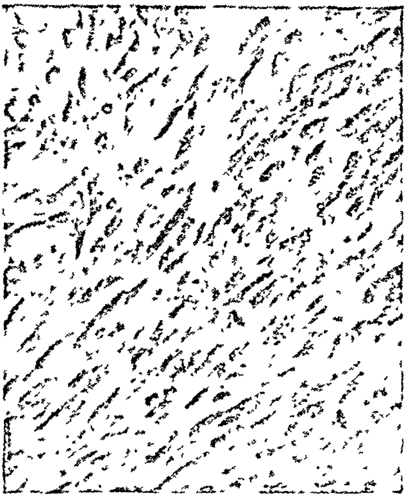


Fig. 8. Photomicrograph—spindle celled type of epidermoid carcinoma showing the presence of several mitosis × 470.

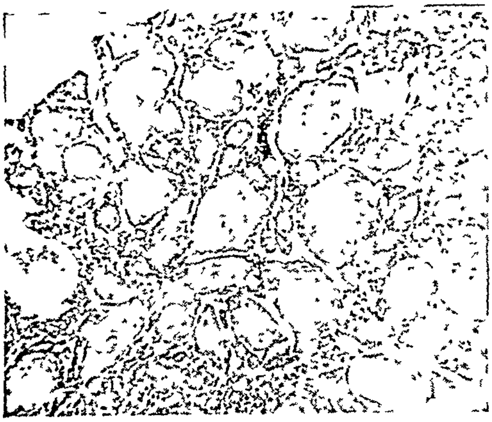


Fig 9 Photomicrograph showing well differentiated keratinised form of epidermoid carcinoma × 60

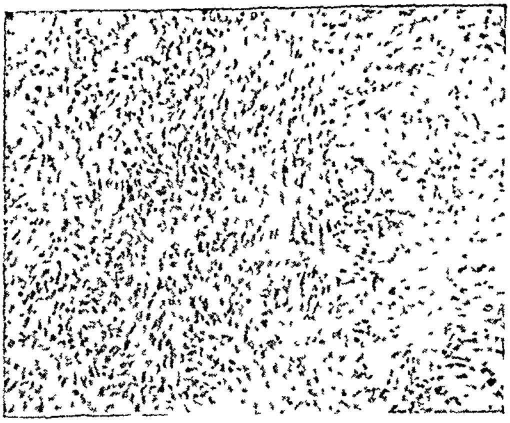


Fig 10 Photomicrograph showing undifferentiated sarcoma like form of epidermoid carcinoma × 110

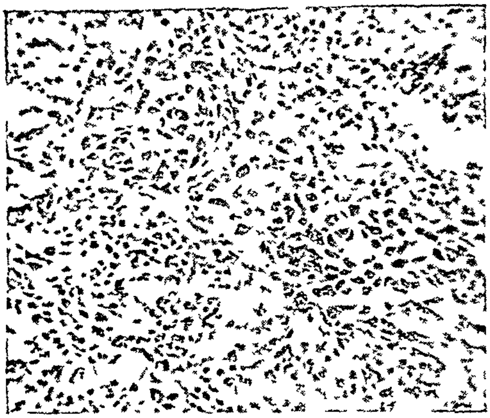


Fig 11 Photomicrograph showing small celled type of epidermoid carcinoma × 230

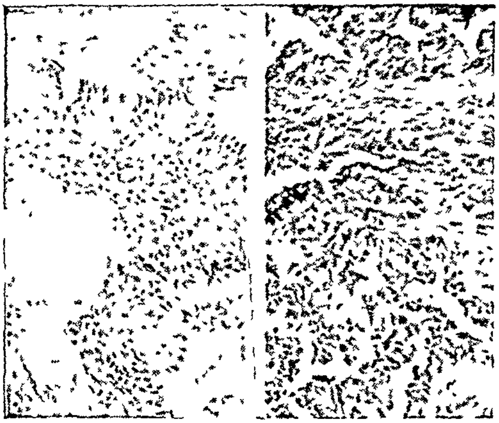


Fig. 12 Photomicrograph of adeno-acanthoma showing typical squamous epithelium with cell nest formation in one area and glandular formation in another

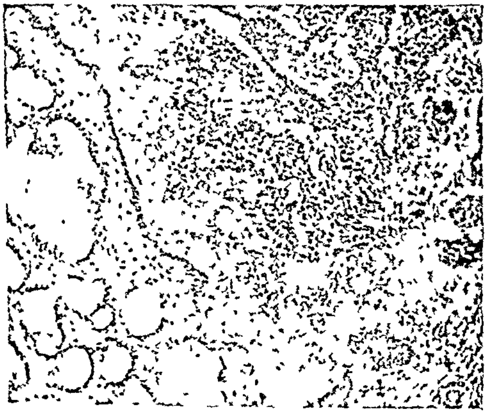


Fig 13 Photomicrograph showing malignant epithelium extending under healthy stratified squamous epithelium × 60

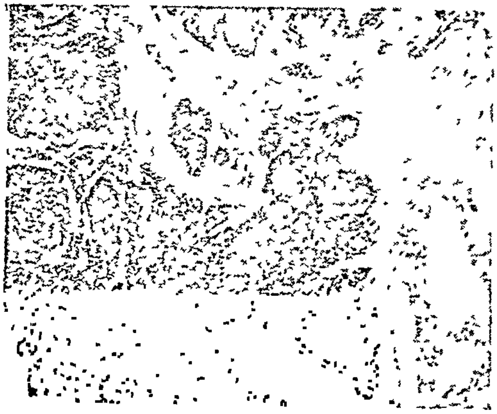


Fig. 14 Photomicrograph showing basal celled type of epidermoid carcinoma × 60.

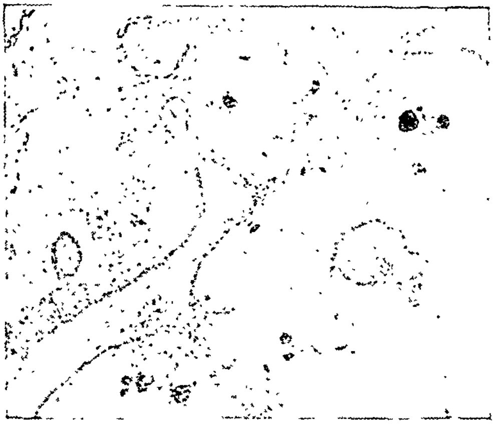


Fig. 15. Photomicrograph showing calcification occurring at the centre of epithelial pearls × 60.

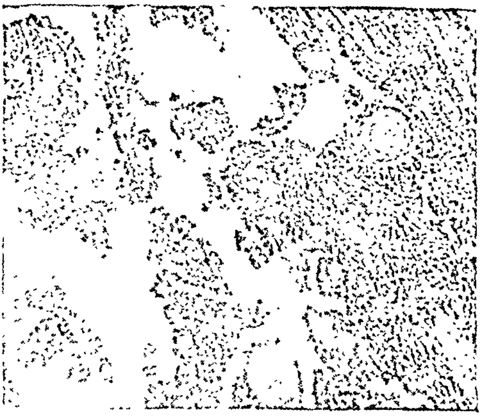


Fig. 16. Photomicrograph showing cell nest formation in a transitional celled type of epidermoid carcinoma × 110.

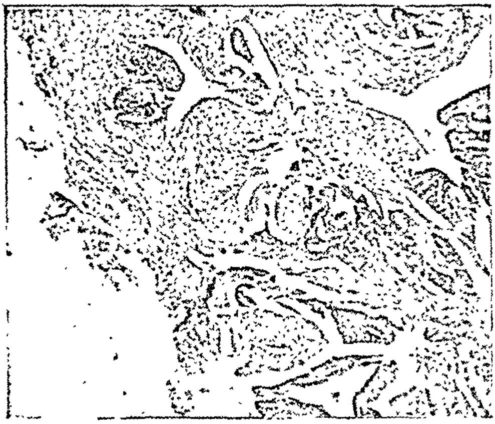


Fig. 17. Photomicrograph—Epidermoid carcinoma resembling scirrhous carcinoma of breast × 110.

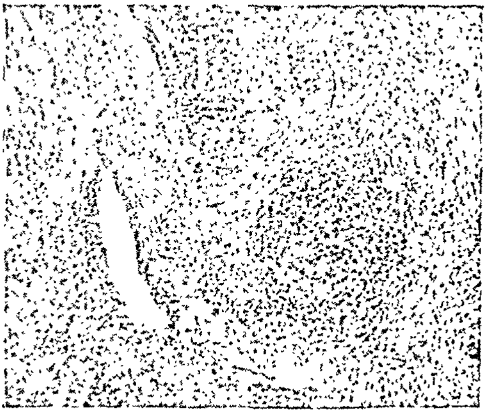


Fig. 18. Photomicrograph of isolated clumps of malignant cells which were the only malignant cells found in the biopsy specimen × 110.

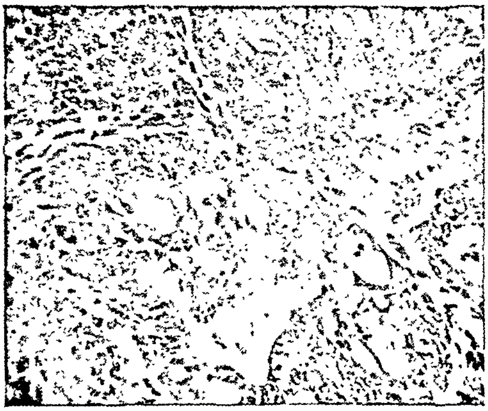


Fig. 19. Photomicrograph showing cribriform type of epidermoid carcinoma × 20.

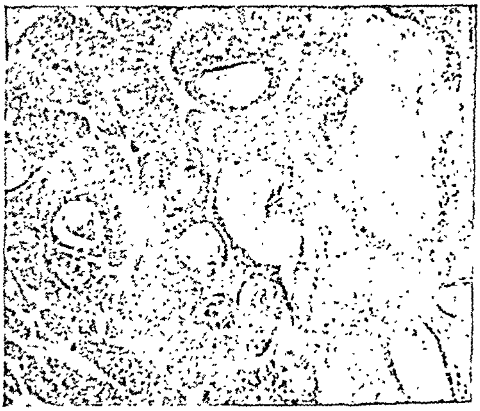


Fig. 20. Photomicrograph showing central degeneration in clumps of malignant cells × 60.

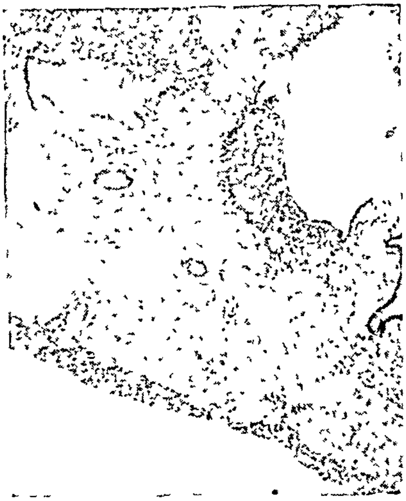


Fig 21. Photomicrograph showing invasion of mucous glands by malignant epithelium × 60.

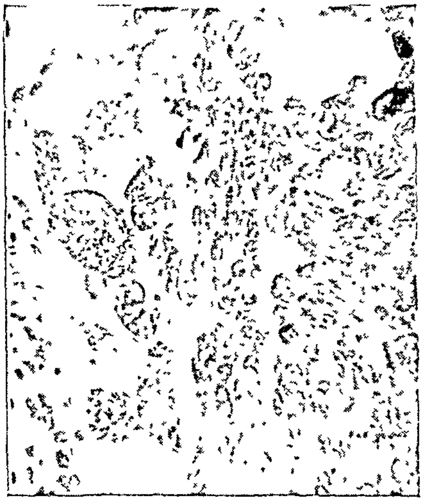


Fig 22. Photomicrograph showing tumour giant cells × 470.

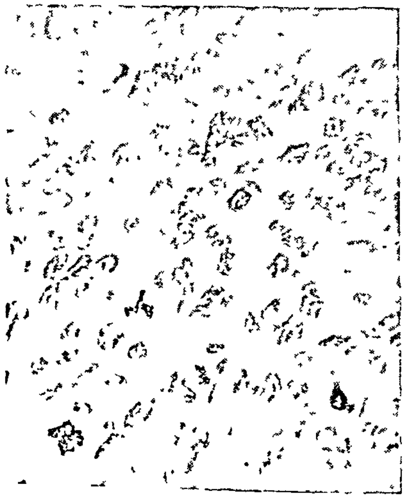


Fig 23 Photomicrograph showing bizarre mitosis following deep X-ray therapy × 470.

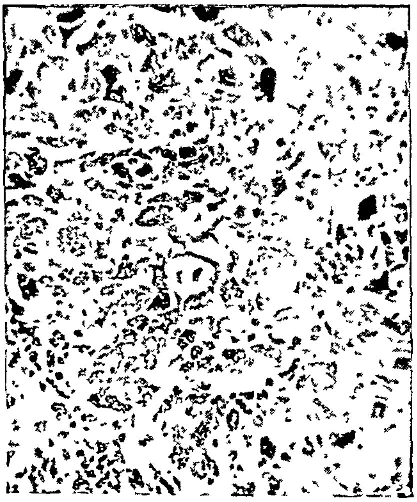


Fig 24 Photomicrograph showing radiation effect on epidermoid carcinoma × 230.

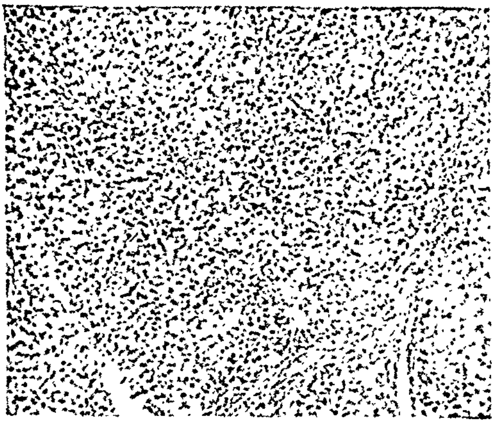


Fig. 25. Photomicrograph showing hydropic degeneration following X-ray therapy × 110.

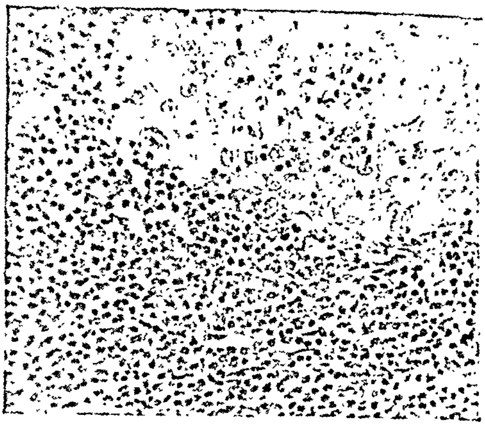


Fig. 26. Photomicrograph showing eosinophilic infiltration of the stroma × 60.

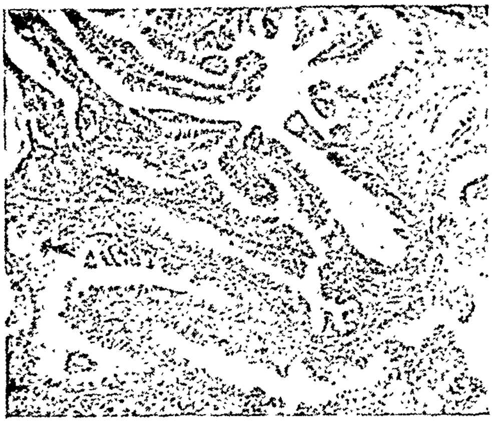


Fig. 27. Photomicrograph—Adenocarcinoma × 60.

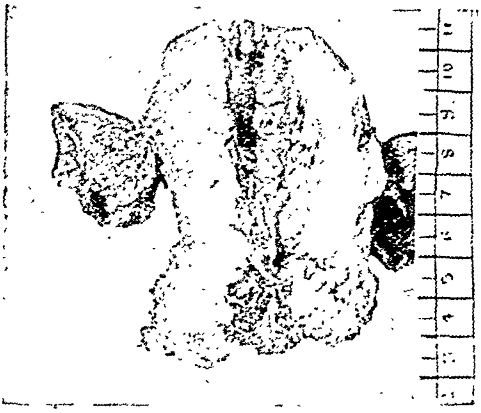


Fig. 28. Macroscopic appearance of a case of adenocarcinoma with destruction of cervix to form a hollow cone.

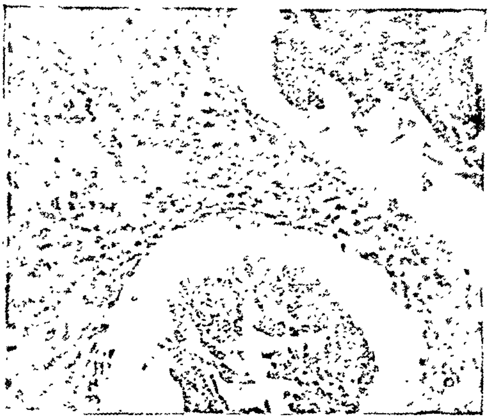


Fig. 29. Photomicrograph showing invasion of veins by malignant cells × 230.

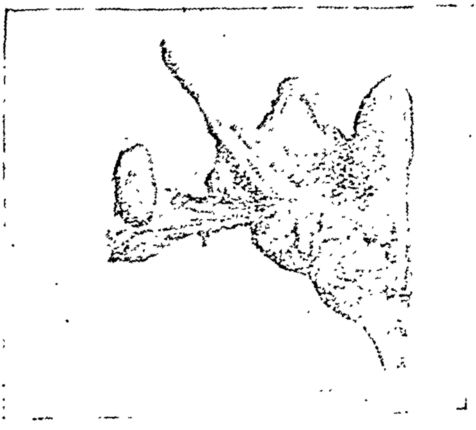


Fig. 30. Macroscopic appearance of carcinoma of cervix showing the involvement of parametrial glands.

carcinoma of the breast (Fig. 17). Such cases may present difficulties in diagnosis. In one case diagnosis had to be made on the solitary clump of cells illustrated in Fig. 18. In a few sections there was a cribriform arrangement resembling that seen in adenoid cystic type of basal celled carcinoma of the skin (Fig. 19). Aschoff[4] has described the frequent occurrence of central necrosis in the islands of cells forming tubes filled with necrotic material and inflammatory cells. This is illustrated in Fig. 20 and should not be confused with adenocarcinoma.

The extension of tumour tissue into the cervical mucous glands is seen in Fig. 21 which closely resembles a drawing in Aschoff's *"L. Pathologische Anatome"*. Willis[35] states that squamous metaplasia of the endocervical epithelium and encroachments of metaplastic epithelium into the cervical glands are common and innocuous and quotes Carmichæl and Jeafferson as observing it in 40 per cent of adult non-malignant cervices.

In some sections large tumour giant cells were seen (Fig. 22). The proportion of mitosis in each section was not determined by accurate mitotic counts but in 154 (29%) they were described as numerous. After deep X-ray the variation in the size of the nuclei usually increases, bizarre mitosis appear (Fig. 23) and many cells show hydropic or fatty degeneration (Fig. 24 and 25).

The stroma varies greatly in amount and may be infiltrated with lymphocytes, plasma cells, neutrophil and eosinophil granulocytes. The latter cells were noted in 35 (6½%) of cases and in several cases the stroma was densely infiltrated with eosinophil granulocytes (Fig. 26). In this case the peripheral blood eosinophil count was only 4 per cent of 9,600 leucocytes.

A typical example of adenocarcinoma of the cervix is illustrated in Fig. 27. These tumours cannot be clearly distinguished from adenocarcinoma of the corpus uteri histologically. Kaufmann[19] dealing with congenital erosions points out that at birth part of the external os is often covered with columnar epithelium and that adenocarcinoma may arise from buried islands of such cells. Aschoff[4] mentions the origin of some of these adenocarcinomata from remnants of the Wolffian duct but does not think the explanation is adequate.

These tumours are typical papillary adenocarcinomata and spread rapidly and early by infiltration of the cervix which often shows no sign on the portio. They may produce destruction of the whole cervix which forms a hollow cone (Fig. 28).

AUTOPSIES

Table 7 tabulates the results of 12 autopsies. A comparison with the figures of Brunschwig[7] on 65 autopsies at the Memorial Hospital, New York; shows that our experience of involvement of the urinary tract

TABLE 7.—*Post-Mortem Statistics.*

1943-50. (12 *Cases*)				New York Figures. 65 Cases in 31 Years.
Hydroureter & Hydronephrosis				
Unilateral	3 cases	one with Pyonephrosis	58%	63%
Bilateral	4 cases			
Uræmia with raised blood urea	5 cases		42%	
Pre-aortic glands involved ..	4 cases		33%	
Bony pelvis involved	1 case		8%	
Infiltration of bladder ..	4 cases	(V.V.F 1 case)	33%	
Distant metastases Ovary..	1 case	Blood borne Metastases Total cases 3	25%	
Lung ..	2 cases			
Spleen	1 case			
Supra-renal..	1 case			
Omentum	1 case			
Kidneys	1 case			
Broncho-tracheal gland	1 case			
Infection : Pelvic Peritoneum	2 cases	Total 4 cases	33%	38%
General Peritonitis	2 cases			
Ascites	3 cases		25%	
Hydrothorax	5 cases		42%	

and death due to sepsis is approximately the same. Salvatore DiPalma[11] in reviewing 124 autopsies considers that sepsis is the most important single factor in fatal cases. Brunschwig also stresses the importance of malignant involvement of the para-aortic glands which we found in 3 autopsies. All authors stress the importance of enlargement of the parametrial and pelvic lymph nodes. Sampson quoted by Ewing[12] states that in 27 cases he found only 10 in which the para-metrium was free. The parametrium may be cancerous while the pelvic nodes are free. It has been our experience to find enlarged pelvic lymph nodes showing evidence of acute inflammation but no malignant infiltration. Willis in 23 autopsies found malignant infiltration of the nodes in twelve. Blood stream metastases is stated by him to have occurred in 25 per cent of the fatal cases but Henrikson[18] gives a figure of 53 per cent in treated and 27 per cent in untreated cases. Our figure is 25 per cent but in only one were there metastases in many organs. In one case there were metastases only in the spleen and lung and in another only in the omentum. In the latter case invasion of veins with malignant tissue could be seen in the section (Fig. 29). Invasion of veins was observed in 6 (1%) of the biopsies. In many biopsy sections the retraction of fibrous tissue away from islands of cells created a false impression of cells lying in vascular spaces. Local infiltration of bones of the pelvis may occur in advanced cases (Fig. 5).

TREATMENT

All the cases in this series were treated with a preliminary course of deep X-ray over a period of three weeks followed by intra-uterine and intra-vaginal radium application according to a modified Curie technique. The swing away from radical surgery to radiation therapy is now being tempered by those who feel that infiltrated glands cannot be adequately dealt with unless removed surgically. Enlarged infiltrated glands are often near the lateral wall of the pelvis and therefore a considerable distance from the cervix (Fig. 30). Meigs[23] advocates a retroperitoneal dissection following X-ray and radium therapy while Read[29] has stated very clearly the indications for surgery. Borges[5] has stated very clearly from his experience at the Tata Memorial Hospital, Bombay, that he found an indication for surgery in a limited number of cases. Nephrostomy for ureteric obstruction was performed on one of our cases.

DISCUSSION

Cancer of the cervix is frequently seen in South India and at present through lack of education patients come for treatment at a very late stage in the disease. The importance of propaganda to encourage patients to seek treatment for any disorder of menstrual bleeding cannot be overemphasised. Maliphant[22] reviewing 1,200 cases discusses the incidence and relative importance of a number of factors. His conclusions have some relevance to our observations. He found however, that menopause had occurred in half the cases while in our series about one third had passed the menopausal age (average 45 years). A comparison with Willis[35] figures suggests that in India carcinoma of the cervix occurs at an earlier age. Maliphant [22] considered that marriage alone doubled the risk of malignancy. Morris and Meigs (quoted by Maliphant) found that marriage before 20 was also a significant factor which would accord with the Indian practice of early marriage. Maliphant contended that the risk varies directly with the number of pregnancies. We were unable to draw any conclusions from an analysis of the number of child-births in our cases.

Regarding the influence of œstrogens our experience is similar to that of other observers that at present there is no direct incriminating evidence. The clinical appearance of carcinoma some years after the onset of menopause or after the birth of the last child, suggests that if the increase of œstrogens in the blood is of etiological importance, its effects must have been produced many years before malignancy manifests itself clinically. The recent work on the duration in which carcinoma *in situ* may remain before spread occurs, is pertinent to this discussion. The work of Ayre[2] on the increased œstrogen fixation and concentration in infected cervical cancers needs more investigation. He also found excess tissue œstrogens in 92 per cent of 50 cervical cancers. He found a deficient urinary thiamine content in 86 per cent of 50 cases of cervical cancer and in only 10 per cent of 50 controls. In

Indian patients in whom vitamin deficiency is common, the above observation may be of ætiological significance. Ayre[2] reports that massive doses of œstrogenic hormone plus large doses of riboflavine causes cancer cells to disappear from the vaginal smear.

The relation of chronic cervicitis to carcinoma is still hotly debated. We were unable to come to any conclusions from our cases although it is true that the cervix is frequently torn in unattended or badly attended cases in India and cervical sepsis and erosion are common. Gagnon[13] claims that the careful treatment of cervicitis is an important measure in preventing carcinoma but naively remarks that in over 4,000 cases of cervicitis treated symptomatically during a period of 17 years, there were no cases of carcinoma. We cannot feel that this treatment could be 100 per cent successful if cervicitis was an important causative factor in cancer. Siebert[33] considers that 75 per cent of cases start in an area of chronic cervicitis but this figure appears to be unduly high.

Our figures agree with Morris and Meigs[23] that bleeding is the commonest symptom and next to it pain which has usually been regarded as a late symptom. They also agree with the work of Maliphant[22] that there is no close relationship between the duration of symptoms and the stage of the carcinoma.

We agree with Willis[35] that a precise grading of the tumours serves no useful purpose as there are many mixed histological types and the transitional celled group covers a very wide range of patterns. Our incidence of adenocarcinoma is lower than that reported by many workers but we have rigidly excluded all cases which presented a pseudoadenoid picture as a result of degenerative changes.

The autopsy figures suggest that radiation therapy alone cannot adequately cope with those cases where glandular infiltration has taken place but this is difficult to assess clinically as glandular enlargement may be due to infection and not always malignant involvement.

SUMMARY

1. Five hundred and forty-nine cases of carcinoma of the uterus diagnosed by biopsy at the Christian Medical College between January 1943 and November 1950 are reviewed. There were 10 cases of adenocarcinoma of the corpus uteri, 14 cases of chorionepithelioma and 525 cases of carcinoma of the cervix uteri.

2. The age incidence is lower than that recorded by workers in America and England. Half the cases occurred between the ages of 30 and 44. The youngest patient was 19 and the oldest 78.

3. All the cases were married except one European patient.

4. Nine patients were nulliparous. The number of patients with 3, 4, 5 and 6 children was about equal.

5. Seventy three per cent of the patients came for treatment five years or more after the birth of the last child. The longest interval was 35 years.

6. In 8 cases (1.5%) carcinoma was associated with pregnancy.

7. Two cases occurred in association with procidentia.

8. One case was found in the cervical stump after supravaginal hysterectomy for multiple fibromyomata.

9. Four per cent of the cases occurred in Muslims. The percentage of Muslims attending the gynæcological department for all diseases was 6.3 per cent.

10. The commonest symptoms were bleeding and leucorrhœa per vaginum and lower abdominal pain sometimes radiating down the thighs.

11. Menopause had occurred in about 1/3 of the cases.

12. The classification into clinical stages can be very misleading. 54.6 per cent of the cases were so classified. 87 per cent of these were in either stage III or IV.

13. The three histological types as described by Marzloff can also be very misleading. Pure spinal 7 per cent and pure spindle 5 per cent are small groups while the transitional celled type forms an indefinite group with marked histological variation.

14. Adenocarcinoma occurred in 7 cases (1.3%)

15. Adenoacanthoma was seen in only one case.

16. Unusual forms were a scirrhus variety, a basal celled carcinoma type, a form like adenoides cystic epithelioma and a small celled variety.

17. Central degeneration in the centre of islands of cells gives a false impression of adenocarcinoma.

18. Apparent extension of the tumour into the cervical glands is probably the result of malignant transformation of metaplastic epithelium.

19. After X-ray therapy sections show huge tumour giant cells, bizarre mitosis and fatty and hydropic degeneration.

20. The amount of the stroma varies greatly. This may be infiltrated with lymphocytes, neutrophil polymorphonuclear cells and sometimes numerous eosinophil leucocytes

21. At autopsy the commonest cause of death is uræmia following uretric obstruction. Pelvic infection is the next most frequent complication. Twelve autopsies are reported. Distant metastases occurred in 25 per cent of cases The para-aortic glands were involved in 25 per cent of cases. In 6 biopsy specimens, veins in the tissue were seen to be invaded by malignant cells.

REFERENCES

1. Arenson, A N.: Clinical Diagnosis of Carcinoma of the Cervix, Radiology 49 400-402, 1947.

2. Ayre, J. E.: Cervical Cancer: A Disordered Growth Response to Inflammation in the Presence of Estrogen Excess and Nutritional Deficiency, Am. J. Obst. and Gynec. **54**: 363-390, 1947.
3. Ayre, J. E.: Diagnosis of Preclinical Cancer of the Cervix, J. A. M. A. **139**: 11-13 1948.
4. Aschoff, L.: Pathologische Anatomie: pp. 610, Jena Verlag Von Gustav Fischer, 1913.
5. Borges, E.; Carcinoma of Cervix, J. Obst. and Gynec. of India **1**: 1, 1950.
6. Balasubrahmanyan, M.: Cytological Diagnosis of Cancer—Accepted for Publication Indian Medical Journal.
7. Brunschwig, A. and Pierce, V.: Necropsy Findings in Patients with Carcinoma of the Cervix. Am. J. Obst. and Gynec. **56**: 1134-1137, 1949.
8. Crosbie, W. G.: Carcinoma of the Cervix after Supravaginal Hysterectomy, Am. J. Obst. and Gynec. **51**: 751, 1946.
9. DeAlvarez, R. R.: The Causes of Death in Cancer of the Cervix Uteri, Am. J. Obst. and Gynec. **54**: 91-96, 1947.
10. De Andrade, G.: Year Book of Obst. and Gynec., Year Book Publishers, Chicago, 1949.
11. DiPalma, S.: Statistical Analysis of 1,637 Cases of Cervical Carcinoma. Am. J. Surg. **79**: 793-799, 1950.
12. Ewing, G.J.: Neoplastic Diseases, 4th Edn., W.W. Saunders, Philadelphia, 1940.
13. Gagnon, F.: Contribution to the Study of the Etiology and Prevention of Cancer of the Cervix of the Uterus. Am. J. Obst. and Gynec. **60**: 516-522, 1950.
14. Galvin, G. A. and TeLinde, R. W.: The Present-Day Status of Non-invasive Cervical Carcinoma. Am. J. Obst. and Gynec. **57**: 15-36, 1949.
15. Given W. P.: Carcinoma of the Cervix, Am. J. Obst. and Gynec. **53**: 947-956, 1947.
16. Graham, M.: The Effect of Radiation of Vaginal Cells in Cervical Carcinoma. I Description of Cellular Changes, II. The Prognostic Signifiance, (Quoted in Am. J. Obst. and Gynec. **54**: 711, 1947).
17. Gusberg, S. B.: The Coning Biopsy, Am. J. Obst. and Gynec. **57**: 752, 1949.
18. Henrikson, E.: The Lymphatic Spread of Carcinoma of the Cervix and of the Body of the Uterus. Am. J. Obst. and Gynec. **58**: 924-942, 1949.
19. Kaufmann: Specialle Pathologische, George Reimer, 1904.
20. Lock, F. L. R., Caldwell J. B. and Winston-Salem, N. C.: The Early Diagnosis of Carcinoma of the Cervix with Emphasis on Routine Biopsy. Am. J. Obst. and Gynec. **57**: 1133-1143, 1949.
21. McManus, J. F. A. and Findley, L.: Histochemical Studies on Glycogen in Carcinoma *in situ* of the Cervix Uteri, Surg. Gynec. and Obst. **89**: 616-620, 1949.
22. Maliphant, R. G.: The Incidence of Cancer of the Uterine Cervix, B. M. J. **1**: 978-982, 1949.

23. Meigs, J. V., Parsons, L. and Nathanson, L. T.: Retroperitoneal Lymph Node Dissection in Carcinoma of Cervix, Am. J. Obst. and Gynec. **57**: 1087-1097, 1949.

24. Morehead, R. P.: Carcinoma in Young Persons, Arch. Path. **38**: 141-146, 1944.

25. Nath, V. and Grewal, K. S.: Indian J. Med. Research, quoted by Willis. **23**: 149, 1935, **24**: 633, 1937, **26**: 785, 1939.

26. Lapan, B.: Deciduosis of the Cervix and Vagina Simulating Carcinoma, Am. J. Obst. and Gynec. **58**: 742-747, 1949.

27. Pohle, E. A.: Radiation Therapy in Diseases of the Female Genital Organ, Chap. V., p. 315, Clinical Roentgen Therapy, 1938.

28. Pollack, R. S. and Taylor H. C., Jr.: Carcinoma of the Cervix During the First Two Decades of Life. Am. J. Obst. and Gynec. **53**: 135-141: 1947.

29. Read, C. D.: The Role of Surgery in the Treatment of Carcinoma of the Cervix Edin. Med. J. **55**: 675-690, 1948.

30. Review of Obst. and Gynec. **8**: 287, 1950.

31. Sadugor, M. G. and Palmer, J. P.: Age, Incidence, and Distribution of 4752 Cases of Carcinoma of the Cervix. Am. J. Obst. and Gynec. **56**: 681-686, 1948.

32. Sadugor, M. G., Palmer, J. P. and Reinhard, M. C.: Carcinoma of the Cervix, Concomitant with Pregnancy. Am. J. Obst. and Gynec. **57**: 933-938, 1949.

33. Siebert, W. J.: Pathological Aspects of Carcinoma Cervix, Radiology **49**: 403-405, 1947.

34. Young, P. A., Hertig, A. T. and Armstrong, D.: A Study of 135 Cases of Carcinoma *in situ* of the Cervix at the Free Hospital for Women, Am. J. Obst. and Gynec. **58**: 867-895, 1949.

35. Willis, R.: Pathology of Tumours—Butterworth & Co., London, 1948.

SOME OBSERVATIONS ON THE "NUTRITIONAL ŒDEMA SYNDROME" †

C. Gopalan and V. N. Patwardhan *

We are presenting certain observations about a syndrome of malnutrition which has received considerable attention in recent years. There has been a good deal of confusion regarding the nomenclature of this syndrome. Cecily Williams[9] who first described the condition designated it 'Kwashiorkor,' an African term which may not be quite applicable to our Indian cases. The Gillmans[3] have called it 'Infantile Pellagra' and quite a controversey has raged over the appropriateness of this name. Trowell[6] in East Africa has described the condition under the term 'Malignant Malnutrition,' but on his own showing, the disease is certainly not so 'malignant' as was at one time believed. Waterlow[8] has called the condition 'Fatty Liver Disease' emphasising a pathological finding which may not be the primary or distinctive feature of the disease. At the risk of adding to this confusion, we in Coonoor have decided to designate the condition as 'Nutritional Oedema Syndrome,' because we consider none of the names in vogue quite suitable, and because we believe that œdema of nutritional origin is the constant, central and minimal feature of the disease.

Before we proceed further, it may not be out of place here to give a short clinical description of the condition which we intend to discuss. The disease is met with in children of the poorest class, usually in the post-weaning period between the ages of 1 and 3 years roughly. The dietary history invariably reveals that the milk intake has been highly inadequate for a considerable period before the onset of the complaint, the diet consisting mainly of rice gruel. The children present œdema of varying degrees of severity but maximal in the dependant parts ; they usually suffer from fatty diarrhœa ; the liver may be enlarged and soft ; the skin of the perineal region and the extremities (particularly at the flexures) often shows a peculiar type of change which has been described as "crazy-pavement dermatosis"; the hair sometimes shows a coppery-red discolouration. The subjects are very apathetic and the voice is often hoarse. Ocular manifestations attributable to vitamin A deficiency—xerosis, Bitot's spots or keratomalacia—are frequently present. Angular stomatitis and cheilitis are less frequent accompaniments. A striking feature in a majority of cases is the evidence of heavy round worm infestation.

---

† Paper read before the First Annual Meeting of the Indian Association of Pathologists in November 1950, at Agra.

* Nutrition Research Laboratories, Indian Council of Medical Research, Coonoor, South India.

Our colleague Dr. P. S. Menon, who has been engaged on this problem will be publishing the detailed results elsewhere. This is a general preliminary report.

During the last two years, we have investigated over 70 cases of this syndrome and our observations this evening are based on this material. Interesting as our clinical and therapeutic observations are, this is hardly the place to describe them in detail. We shall mainly confine ourselves to problems of 'pathological' or 'clinico-pathological' interest. We shall here deal briefly with the hepatic, pancreatic and cutaneous changes and also touch on certain biochemical findings of interest.

Liver :—We have started doing routine serial liver biopsies in our cases only recently and as such our remarks can only be tentative. The histological appearance of the liver before treatment was as follows. The lobular pattern was well maintained. The liver cells were seen to be distended by fat and the nuclei were pushed to one side. The sinusoids were inconspicuous because of the crowding out by the distended cells. The central veins appeared normal and in their normal position. The periportal connective tissue was increased to varying degrees in different cases and was markedly cellular, the cells being mostly lymphocytes and fibroblasts. In some cases, the periportal connective tissue was seen extending from the portal tract in a perilobular fashion.

Biopsy of the liver repeated after five to six weeks of intensive high-protein therapy revealed a marked regression in the fatty change but there was no appreciable change in the peri-portal connective tissue proliferation. We expect that the follow-ups of longer duration which we are now attempting, may throw light on the evolution of the pathological process and on the possible relationship of this syndrome to portal cirrhosis of adults. We have not been able to substantiate Davies'[2] claim that the disappearance of fatty change under protein treatment is characterised by a gradual "retreat of fat from the centre to the periphery". It is our finding that the diminution of fat, under protein therapy occurs simultaneously over the entire lobule in a uniform manner rather than regionally as suggested by Davies.[2]

In a few cases, there was also evidence of necrotic changes in groups of liver cells scattered irregularly in the parenchyma ; the cell outlines had disintegrated and the nuclei had become pyknotic and deep-staining. This evidence of patchy necrosis was particularly noticeable in livers with minimal fatty change after high-protein therapy. It was not apparent in livers with advanced fatty infiltration. It is possible that the necrotic changes had become more apparent after the subsidence of the fatty change. On the other hand, it has been claimed by some workers that fatty infiltration of the liver inhibits necrosis.

In conclusion, the predominant and uniform findings in the liver in these cases are fatty infiltration of the cells and connective tissue proliferation in the periportal areas.

We have been particularly interested in the histological appearance of the liver from the point of view of prognosis. Just at present, there are no clinical or biochemical signs which could give us an indication of the probable termination of a given case. In our experience, the severity of the œdema, the dermatosis, etc., are misleading indications. Trowell[6] has claimed that the severity of fatty infiltration as judged by the histological appearance was an index of the severity of the case. In our limited experience, we found that the degree of fatty infiltration bore no relationship to the severity of the œdema or the serum albumin level nor did it indicate the prognosis. Under identical treatment we have had fatalities among cases showing minimal fatty change and recoveries among cases showing extensive fatty infiltration.

Before concluding the observations on the liver changes, the question of the relationship of this syndrome to the condition known as infantile biliary cirrhosis may be referred to. We believe that there is no parallelism either with regard to clinical features or from available evidence, with regard to histopathological features between these two conditions. We are, therefore, of the opinion that infantile biliary cirrhosis is distinct and different from the nutritional œdema syndrome. In Coonoor where we see a fair number of cases of the nutritional œdema syndrome, we do not see many cases of infantile biliary cirrhosis.

Pancreas :—Davies[2] and Waterlow[8] have described changes in the pancreas in this syndrome and have indeed suggested that these changes may well constitute the primary lesion. According to Davies,[2] the pancreas may show in advanced cases: perilobular and periductal fibrosis, disappearance of acinar tissue and sometimes even of the islet tissue. We have been able to study the pancreatic changes only in one case on which we could perform autopsy. The findings were indeed striking. The pancreas was hard and resistant to cut. Histological examination revealed well-marked perilobular, periductal and interstitial fibrosis and the acinar pattern appeared distorted. The islet tissue was not to be seen.

The changes in the islet tissue are indeed interesting. A common terminal event in our cases which ended fatally, was convulsions; because of the steatorrhœa we investigated the possibility of tetany in these cases but found the serum calcium within normal limits and parenteral calcium therapy was of no avail. We hope to investigate the possibility of a hypoglycæmic basis in these cases because Davies[2] claims that the islet tissue actually shows hyperplasia preceding the atrophic change.

The Dermatosis :—Next we shall proceed to discuss the skin lesion which is characteristic of the full-fledged syndrome. This has been called crazy-pavement dermatosis and there has been some confusion regarding its significance and its relationship to adult pellagrous

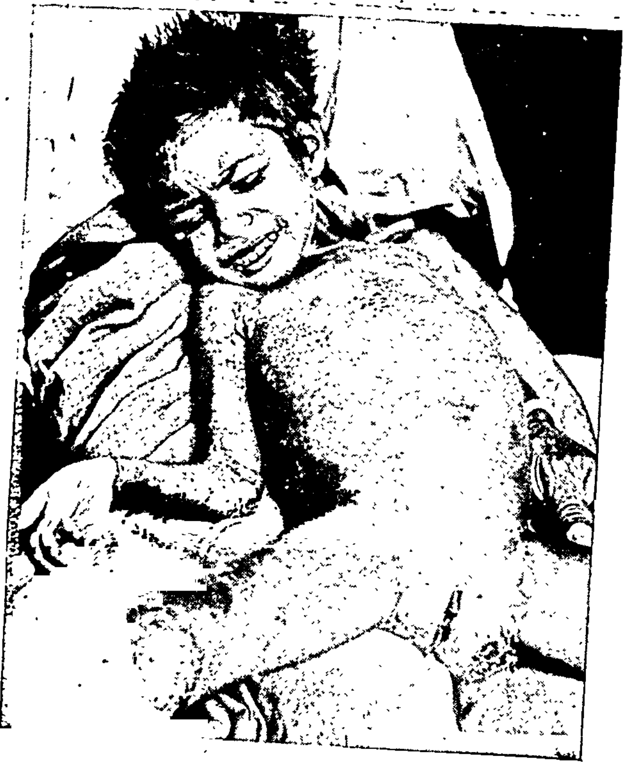


Fig. 1. Photograph of a case of "Nutritional Oedema Syndrome" presenting the characteristic dermatosis.

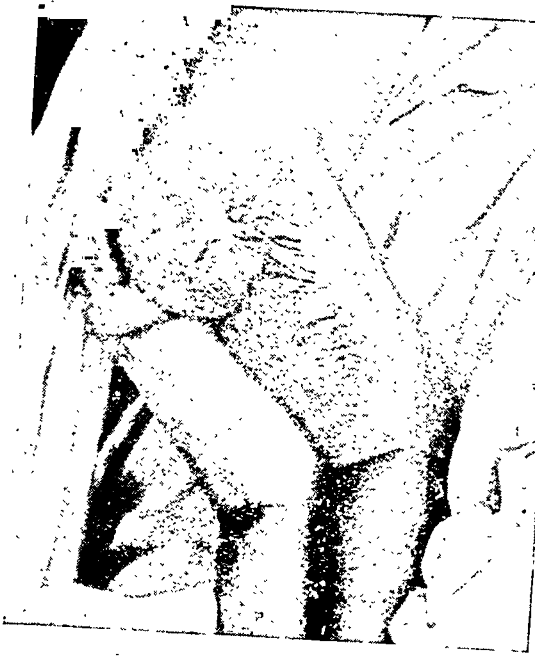


Fig. 2. Photograph showing crazy-pavement dermatosis.

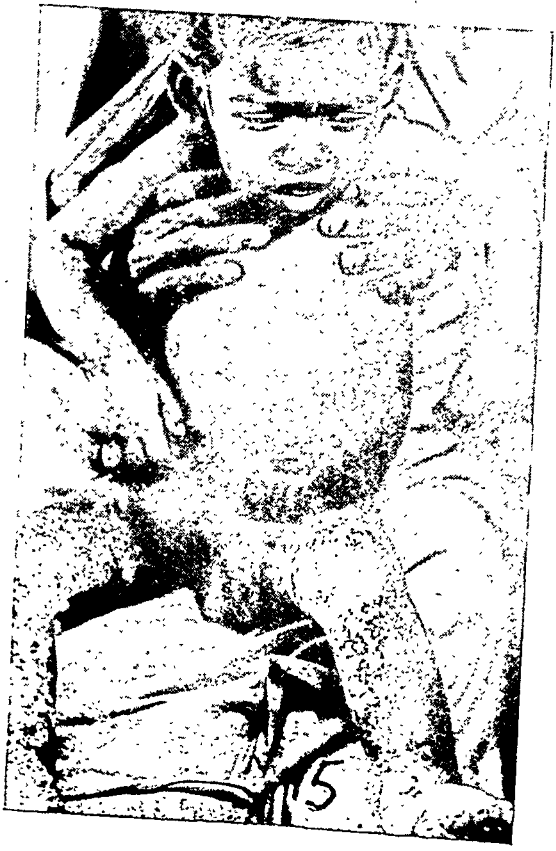


Fig. 3. A case of "Nutritional Oedema Syndrome" presenting the characteristic dermatosis.

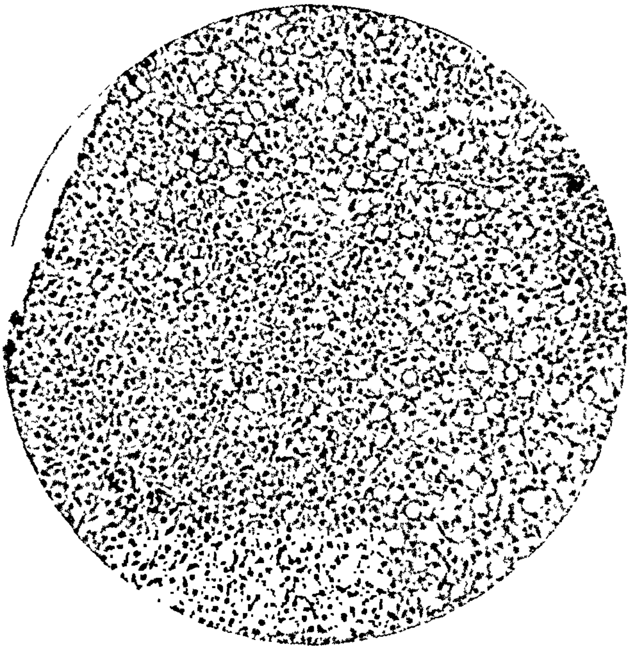


Fig. 4. Photomicrograph of liver showing fatty infiltration of cells.

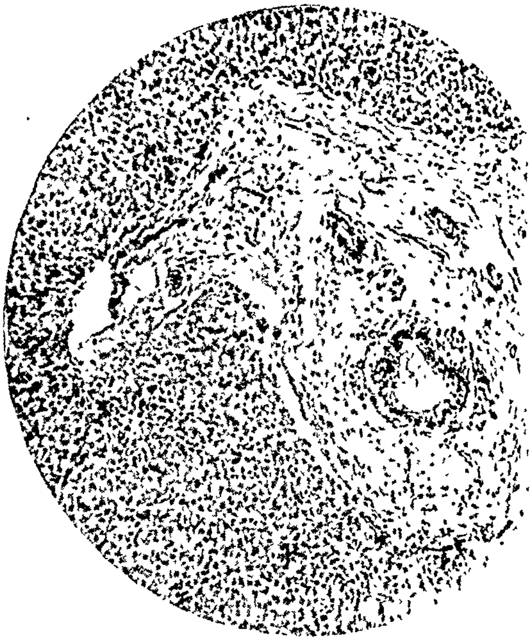


Fig. 5. Photomicrograph of liver showing c nective tissue proliferation around portal tr

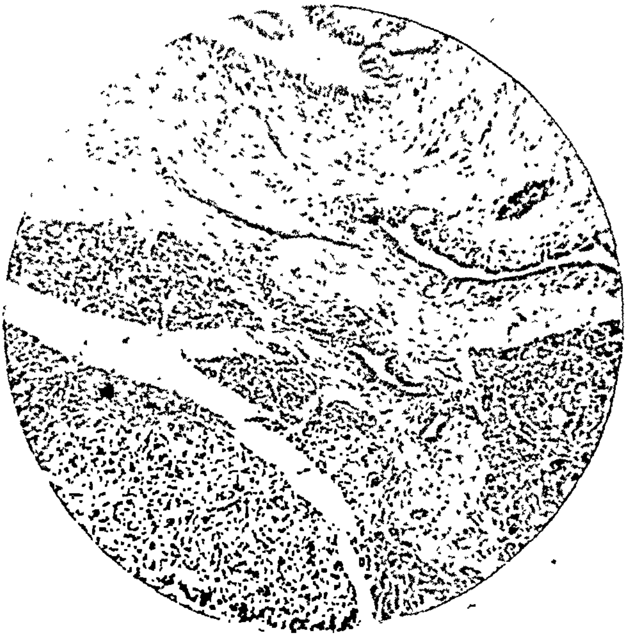


Fig. 6. Photomicrograph of a section of pancreas showing extensive fibrosis

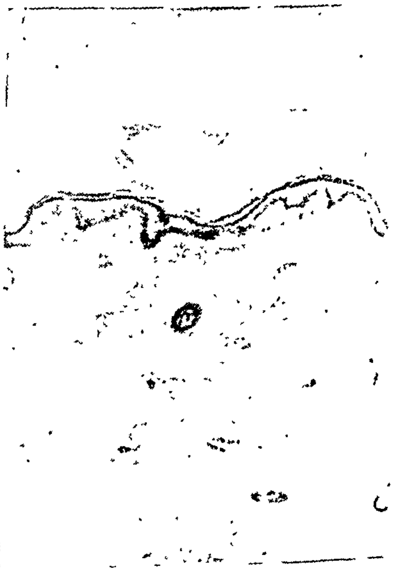


Fig. 7. Photomicrograph of a secti of skin showing crazy-pavemen dermatosis.

dermatitis. It was the presence of this dermatosis which suggested the term 'Infantile Pellagara' to this syndrome. We believe that these skin lesions are certainly 'pellagrous' in nature but they constitute only an incidental and relatively insignificant complication.

The skin lesion starts as well-defined black patches over certain parts of the body. These patches may vary in size but they have a fairly common distribution in all cases—the perineal region, the region over the ischial tuberosities and trochanters and the popliteal and cubital flexures; in advanced cases the trunk is also affected. Sooner or later these black patches crack and separate in large flakes from the subjacent skin, which appears pale and thin.

The dermatosis is apparently different in distribution and evolution from adult pellagrous dermatitis. But histological examination reveals that in both cases there is the same thickening of the stratum corneum, increased pigment in the basal layer, absence of sebaceous glands and atrophy of the sweat gland. Crazy pavement dermatosis is thus essentially identical to adult pellagrous dermatitis but clinically it runs a more dynamic course.

As has already been mentioned the occurrence or extent of the dermatosis is no indication of the prognosis of the case. Treatment with 'B' vitamins has been shown to cause regression of the skin change but this may aggravate the other manifestations. So in the treatment of these cases we concentrate on the supply of adequate quantities of easily assimilable proteins and do not rely on synthetic vitamins singly or in combination.

Biochemical Changes:—We shall next deal with certain chemico-pathological aspects of the disease. The plasma proteins as determined by the microkjeldahl method were found to be low, the average in 20 cases being 3.89 Gm. per cent. After treatment with high-protein diet for five to six weeks, there was an appreciable rise in the level of plasma proteins, the average level in 18 cases being 7.04 Gm. per cent. By employing the method of fractional precipitation we are now determining the levels of the albumin and globulin fractions before and after treatment. The results obtained so far indicate that the fall in plasma proteins involves both the albumin and globulin fractions, but the fall in plasma albumin is more pronounced. It is interesting that the globulin level in these cases of protein deficiency was actually lower than normal and that under treatment there was a rise in the level of both the albumin and globulin fractions. Much confusion still surrounds the subject of the actual significance of the serum globulin level. High values for serum globulin have been reported in adult cases of protein deficiency among Africans, while among African children suffering from malnutrition, the reported values for serum globulin are either normal or subnormal in a majority of cases. How far the high serum globulin of African cases of malnutrition is the result of associated parasitic infestation is a very important consideration. A suggestive observation in this connection is that the rise in globulin in these cases is mainly attributable to the gamma fraction, which is mainly concerned with immunity response. There seems no reason to expect that in an uncomplicated case of protein deficiency the globulin fraction may rise.

It is, however, necessary that these plasma protein figures are interpreted with caution. The changes in plasma volume in œdema and the effect of high-protein treatment thereon, are bound to cause apparent fluctuations in the plasma protein level. Lusk has shown that there is hydræmia in hunger œdema and Dent has shown that with high-protein therapy this hydræmia is reversed. How far the low serum protein level seen before treatment is the result of hydræmia and how far the rise in serum protein after treatment is the effect of reduction of plasma volume are still moot questions. This aspect of the problem seems to have been completely missed by all the workers who have commented on the serum protein figure in this disease.

Lipase and Esterase :—We have already indicated that lesions of the pancreas constitute an important pathological feature of the disease. Vaghelyi[7] has reported that in protein deficiency the exocrine activity of the pancreas suffers owing to degenerative changes in the acini. As biochemical proof of this Vaghelyi[7] has shown that the concentration of some pancreatic enzyme in the serum of patients with this disease was low and that it was restored to normal after high-protein diet therapy. We have investigated this question with regard to two enzymes—plasma lipase and plasma esterase. The plasma lipase was determined by the method of Goldstein *et al*[4] and plasma esterase by that of Cherry and Crandall.[1] In 17 cases before treatment the average plasma lipase value was 37.2 units. After high-protein therapy there was a marked rise in plasma lipase values in all cases, the average in 20 cases being 144.3 units per 100 c.c. If, as is generally believed, the plasma lipase originates in the pancreas, the two values before treatment may be indicative of deficient pancreatic function or of defective absorption or of both. Recently, some doubt has been thrown by Seligman and Nachlas[5] on the specificity of plasma lipase estimations by the method which uses tributyrin as the substrate—which is the method we had adopted. We are reinvestigating this question in the light of this observation and would, therefore, refrain from drawing conclusive figures for the present.

We also found a low plasma esterase value in our cases before treatment and a distinct rise after treatment. The average plasma esterase value in 21 cases before treatment was 77.7 units per 100 c.c. and in 22 cases after treatment 161.1 units per 100 c.c. Low plasma esterase values suggest a deficient liver function. Apart from the abnormal histological picture presented by the livers in nutritional œdema syndromes, Holmes and Trowell[6] have demonstrated failure of liver cells from biopsy specimens, to store glycogen in the presence of liberal amounts of glucose. Waterlow[8] has found lowered choline esterase activity of biopsy specimens of the liver in two cases. In the light of these observations, the appreciable difference in our plasma esterase values in the same cases before and after treatment appear significant. But the very wide range of figures deprives them of diagnostic utility. We hope, however, that they may be of help in assessing the prognosis and therapeutic response of cases. Studies aimed at correlating biopsy findings with biochemical findings may, we expect, throw further light on the true significance of the histopathological and biochemical findings which we have discussed above.

CONCLUSION

We have attempted to cover a rather wide field in these few minutes. The problems presented by the disease which we have called Nutritional Oedema Syndrome are so multifarious and multisided that we have not been able to avoid several important gaps in this paper. For instance we have not discussed the significance of the anæmia or the steatorrhœa which are important features of the disease. We have omitted the consideration of the important question of the pathogenesis of œdema, which has been engaging our attention in Coonoor. We have also not raised the fascinating and important question of the ætiological role of round worm infestation in this disease—a subject on which we have already obtained some interesting evidence in our laboratories.

REFERENCES

1. Cherry, I. S. and Crandall, L.A.: Specificity of Pancreatic Lipase, Its Appearance in Blood after Pancreatic Injury, Am. J. Physiol, **100** : 266-273, 1932.
2. Davies, J. N. P.: Essential Pathology of Kwashiorkor, Lancet, **1** : 317-320, 1948.
3. Gillman, J. and Gillman, T.: Powdered Stomach in Treatment of Fatty Liver and Other Manifestations of Infantile Pellagra, Its Significance with Reference to Problems of Oedema and Steatorrhoea in Infants and Adults, Arch, Int. Med. **76** : 63-74, 1945.
4. Goldstein, N.P., Epstein, J.H. and Roe, J.H.: Studies of Pancreatic Function, J. Lab. and Clin. Med., **33** : 1047-1051, 1948.
5. Seligman, A.H. and Nachlas, M.M.: The Colorimetric Determination of Lipase and Esterase in Human Serum, J. Clin. Invest., **29** : 31-36, 1950.
6. Trowell, H.C.: Malignant Malnutrition (Kwashiorkor), Trans. Roy. Soc. Trop. Med. & Hyg., **42** : 317-442, 1949.
7. Vaghelyi, P. V.: Pancreatic Function in Nutritional Oedema, Lancet **1** : 497-498, 1948.
8. Waterlow, J.C.: Nutritional Liver Disease in West Indian Infants, Proc. Roy. Soc. Med. **40** : 347-351, 1949.
9. Williams, C.D.: A Nutritional Disease of Childhood, Associated with a Maize Diet, Arch. Dis. Chil. **8** : 423-433, 1933.

FALSE POSITIVE SEROLOGICAL REACTIONS FOR SYPHILIS†

Balbir Singh *

The problem of biologic false positive serological reactions for syphilis has not assumed as much importance in our country as in America where food handlers, pregnant women, those who intend to marry, individuals called up for service or released from the army and those employed in certain industries have to get themselves serologically tested; it is however a matter of sufficient concern, for the pathologists who are responsible for these tests in laboratories attached to teaching institutions or in the laboratories of the Armed Forces, as many a time the tests are asked for just to exclude syphilis though there is no suspicion on clinical grounds and some of these patients are suffering from diseases that give rise to false positive serological reactions.

Elimination of these reactions is of great importance to an individual because of the social and psychological tragedies this diagnosis sometimes precipitates. It is important to the state as it involves heavy expenditure to treat for syphilis a large number of cases who are really not suffering from it. Kahn[5] estimated 65,000 such cases in America on the basis of 0.05 per cent false positive serological reactions found in his test during the official evaluation studies. I should not be much surprised if the false positive rate of most laboratories in India is much higher.

Observations on false positive serological reactions for syphilis were, in fact, made soon after Wassermann had published his original technique for the complement fixation test. It was observed in Wassermann's laboratory that the sera of some monkeys gave a positive result. Neisser's monograph on the pathology and therapy of syphilis published in 1911 (that is five years after the publication of the Wassermann reaction) included a chapter by Bruck on the Wassermann reaction in non-syphilitic individuals. He referred in that chapter to false positive reactions observed by other workers in yaws, leprosy, trypanosomiasis, malaria and to a lesser extent in some other diseases.

There has been a gradual uncovering of the diseases giving rise to non-specific reactions. Stokes[16] listed seventy-three such diseases on the basis of personal observations and reports by other workers. This ever increasing list of the clinical conditions causing false positive reactions, normal individuals showing biologic false positive reactions and the duration of these reactions varying from a few days to several years or a life time, have shaken the confidence of the present day syphilologist's in a positive report. It is no longer considered justified to label somebody as syphilitic on the basis of only a positive serological test for syphilis.

---

† Paper read before the First Annual Meeting of the Indian Association of Pathologists in November 1950 at Agra.

* Department of Bacteriology, Irwin Hospital, New Delhi.

With a view to determine the factor or factors responsible for these reactions the sera of animals were examined by some workers and they reported false positive reactions in various animals, *viz.*, rabbits, horses, cows, sheep and chicken.

Others demonstrated non-specific reactions by variously modifying the sera, the antigen or the technique of the test. Their work did not clarify the paradoxical problem of the serology of syphilis except that it showed that there were many substances, *viz.*, dehydrating agents like alcohol and various electrolytes including acids and various salts that could flocculate the antigen suspension. These substances are so commonly found in any laboratory that it was considered necessary to exclude the possibility of a false positive serological reaction due to adventitious material in the antigen suspension before labelling the reaction as biologic false positive.

Kahn[6] and his co-workers showed precipitation in mixtures of non-syphilitic serum and antigen suspension by ultramicroscopic studies though it was not visible to the naked eye. It was concluded by them that precipitation took place in mixtures of non-syphilitic serum and antigen suspension but not to the same degree as in mixtures of syphilitic serum and antigen suspension. If the antigen was slightly modified, the aggregates with the non-syphilitic serum could become big enough so that they would be visible to the naked eye and could become even bigger than those produced by mixtures of syphilitic serum and the standard Kahn antigen. They further concluded that the precipitation reaction as a result of mixing serum and the antigen suspension was not limited to syphilitic sera. The basic reaction was a biologic manifestation found universally amongst animals and human beings and the modern serological tests could be so modified as to give positive reaction indiscriminately in the absence of syphilis. The universal reaction suggested that it might have something to do with the false positive reactions given by serodiagnostic tests and it also emphasised the fact that in the serology of syphilis we were dealing with a test which was primarily not specific for syphilis. Further work by Kahn[6] showed that precipitation with sera of animals was more marked at 1° C. than at 37° C. This observation was applied to sera from individuals who were presumed to be showing biologic false positive reactions. It was found that positively reacting serum of non-syphilitic human beings behaved like positively reacting serum of non-syphilitic animals. This type of behaviour by non-syphilitic sera was called by Kahn, "General biologic (false positive) type of reaction", and he proposed a test which he called 'verification test' on the basis of these observations, to differentiate false positive reactions from syphilitic reactions. Unfortunately appraisal of this test by independent workers showed some inconsistencies. They concluded that the test was of help in some cases, as for example, when the complement fixation test was negative and the Kahn test was positive but it unexpectedly showed a general biologic type of reaction in patients with known syphilis and a syphilitic type of reaction in some non-syphilitic. On the basis of further work he proposed another verification test called the triple quantitative test. But this test also was not confirmed by others. Efforts have been made by numerous workers to produce an antigen with improved specificity, *i.e.*, an antigen which does not give false positive reactions. Consequently several different tests or techniques came into existence but none of them is free from false positive serological reactions or has a hundred per cent specific sensitivity. Antigens prepared from cultures of *Spirochæta pallida* were investigated. Variable results were reported by different workers. Kolmer[7] and his co-workers showed that in addition to the antibodies for the *Spirochæta pallida* there is an antibody especially for *S. microdentium* found naturally in a large percentage of normal non-syphilitic sera. This is a group antibody and results in a large percentage of non-specific complement fixation reactions with the antigen of *Spirochæta pallida*. It was also concluded at the Washington serological conference in 1940 that the so called specific antigens gave false positive reactions. The general consensus of opinion has been that spirochætal antigens are inferior to alcoholic tissue extracts re-enforced with cholesterol.

During the present decade however, research in improving the antigen produced some important results. Mary Pangborn[11] of the New York State, Health Department, isolated a phospholipid from the alcoholic heart extract. This purified phospholipid along with lecithin and cholesterol has already proved to be a more sensitive antigen for both the complement fixation and the precipitation tests, than the alcoholic heart extract. It was hoped that this antigen would eliminate false positive reactions. This hope however was not justified, though it has been claimed that cardiolipin antigens show a smaller number of false results.

Some immunological aspects of the reagin or the antibody in the syphilitic sera fixing complement or the flocculating antigen in precipitation tests were also studied but they did not help to clarify the problem of false positive reactions. Nelson and Mayer[9] published last year a technique to identify antibodies produced in syphilitic infection by immobilisation of virulent *Treponema pallidum in vitro*. They used virulent cultures of *T. pallidum*, separated from the testis of a rabbit previously inoculated intratesticularly. Antigen prepared from a suspension of these spirochætes when mixed with syphilitic serum in the presence of guinea-pig serum immobilised the spirochætes. Normal human serum did not show antibodies which could immobilise the *Treponema pallidum.* Unfortunately such a test will not be within the scope of every laboratory unless live cultures of spirochætes are made available from a central laboratory.

Most promising however has been the work of Neurath[10] and his co-workers. They isolated the immune bodies or antibodies from the serum in the form of euglobulins and set up a precipitation test with the euglobulin solution in the presence or absence of crude albumen solution. They found that the albumen solution inhibited the serological activity of euglobulin fractions derived from human sera showing false positive reactions. It is a rather complicated procedure for an ordinary laboratory but it is hoped that these workers will be able to produce a simpler method on the same basis to differentiate syphilitic from non-specific reactions.

INCIDENCE OF FALSE POSITIVE REACTIONS

Normal and apparently healthy individuals :—Eagle's[2] figures were 1 in 4000 amongst 40,540 college students tested by him in 1941. Greene, Breazeale and Andes[3] found 1.66 per cent positive or doubtful amongst 5,000 college students during the same year. After these reports no other survey has been reported but a number of individual cases have been reported and the present consensus of opinion amongst clinicians of long standing in America is that they are now meeting a larger number of cases in which they have sufficient reasons to doubt the positive serological report. They are not sure whether the increase is real or is a relative one in relation to syphilitic patients as more patients are now becoming seronegative because of modern antisyphilitic treatment than they did under the old regime. Some of these clinicians are questioning the high prevalence figure for syphilis among Negroes as most of them show no evidence of a primary lesion and nor is there an equally high frequency rate of congenital syphilis amongst them. Recently an inquiry was instituted to study the high incidence of positive serological tests for syphilis in the absence of clinical manifestations amongst the Indians of Guatemala. There are similar communities elsewhere in America to whom this investigation is likely to be extended if any useful information comes forward from the inquiry at Guatemala.

DISEASES AND OTHER CONDITIONS RESPONSIBLE FOR FALSE POSITIVE REACTIONS

Yaws, Begel and Pinta :—As these diseases are caused by organisms indistinguishable from the *Spirochæta pallida* and also respond to anti-syphilitic therapy, the positive serological reactions amongst them should not be considered false for all practical purposes. Moreover they are of importance only in the localities where they are endemic.

Leprosy :—False positive reactions in leprosy are of practical importance to the clinicians in India as most of them must have known cases of leprosy that were labelled and treated as syphilis on the basis of positive serological tests. It is not possible to go into the wide variety of figures reported by different workers, but, *survey conducted by us at* the Leper hospital, Colombo, Ceylon, showed positive or doubtful W.R, and/or Kahn test in 51.56 per cent in both lepromatous and neural cases of leprosy. The Wassermann reaction was positive or doubtful in 40.5 per cent and the Kahn test *was positive or doubtful in 42.1 per cent.* It has been believed by some clinicians that the Kahn test does not give false positive reactions in leprosy. This belief was obviously based on the work of Yagle and Kolmer published in 1923. Their observations were based on a small series of sera and were not confirmed by latter workers. Some workers reported a lower percentage of positive Kahn tests in leprosy than of the W. R. during the twenties. This might be due to the low sensitivity of the Kahn antigen at that stage.

Malaria :—This disease is important as a cause of false positive serological reactions because it is so prevalent in India and specimens of blood for serological tests are often received in laboratories attached to hospitals from patients suffering from 'fevers" or "P.U.O." or sometime after they have suffered from fever. There have been reports varying from flat negative to 100.0 per cent. Most of the recent workers however have reported false positive reactions in malaria and those working on induced malaria, especially if they had facilities to examine blood frequently, reported percentages as high as 100.0 at one stage or other of the disease. A survey conducted by me during the time I was in charge of the army serological laboratory in Ceylon showed positive W. R. and/or Kahn test in 38.6 per cent of 122 cases investigated. The corrected positive rate for malaria was 27.3 per cent, as 11.3 per cent of the hospital population not suffering from malaria showed positive W.R. and/or Kahn tests. The proportion of false positive reactions was the same with the Wassermann reaction and the Kahn test. Temperature had no relation to false positive serological tests. In fact those reactions were observed by those who investigated false positive reactions in induced malaria before the onset of fever in some cases. Most false positive results were observed by me at the end of the first week but one case had a doubtful and another had a positive W.R. on the 26th and 30th day respectively.

Eosinophilia :—False positive reactions in eosinophilia were first pointed out by Greval.[4] I was able to study serological tests in 16 cases of eosinophilia. The combination of a positive Wassermann with a negative or doubtful Kahn was a characteristic feature of these reactions. Eosinophils below 16.0 per cent were not associated with false positive reactions but four out of five cases that had a 30.3 or higher percentage of eosinophils showed false positive serological tests.

Small pox vaccination :—During the last war a number of reports on false positive reactions after small pox vaccinations were published. Observations on 42 cases were recorded by me in the army serological centre. 14.3 per cent showed positive or doubtful W. R. and/or Kahn test. These reactions were observed only in those who showed non-immune or accelerated reaction and disappeared usually in two months time but persisted up to four months in some cases.

Pneumonia and respiratory infections :—These are mentioned as important causes of false positive serological reactions by most American authorities. I have no figures to quote from my own work except that lobar pneumonia showed a higher percentage of positive or doubtful results than the rest of the hospital population. The other cases with respiratory symptoms that repeatedly showed positive or doubtful W. R. and/or Kahn test in the absence of clinical evidence were diagnosed ultimately as tropical eosinophilia.

Primary atypical pneumonia :—There were a number of reports on false positive serological reactions for syphilis in primary atypical pneumonia during the last war.

Tuberculosis :—There have been varied reports. Evidence that appears to be reliable was brought forward by Dunner and Mayer[1] who did post mortem examinations on twelve out of thirty one-cases showing presumably false positive reactions. None of them showed any evidence of syphilis. They observed negative serological reactions changing to positive with the advance of the disease. Observations made by me in the army serological centre in Ceylon showed no conclusive evidence of false positive reactions in pulmonary tuberculosis except that a Ceylonese boy, eight years old, admitted to Chest hospital, Colombo had positive serological tests on repeated examinations. He showed no stigma of congenital syphilis, nor was there any evidence of the disease in his family history.

Other conditions:—Infectious mononucleosis, rat bite fever, lymphogranuloma venereum, relapsing fever, kala-azar and lupus erythematosis are other important diseases mentioned as causes of false positive serological reactions. Acute exanthemata like measles, chicken pox and scarlet fever, natural or induced fever, subacute bacterial endocarditis, leptospirosis and typhus fever are some of the other diseases in which false positive reactions have been reported.

CONCLUSION

I have briefly gone over the recent progress made in differentiating false positive serological reactions from true reactions. I have mentioned the incidence of these reactions in normal and apparently non-syphilitic individuals and in diseases which I had the opportunity to investigate. Those of you who are interested in the procedure that you should follow in a suspected case of biologic false positive may please refer to an article by Moore, Eagle and Mohr.[8] Briefly, they recommend that one should withhold treatment and carry out a prolonged serological follow-up for weeks or months. It is preferable to do quantitative tests as a falling titre without treatment means a false positive reaction. If the titre is sustained or increases it is not likely to be a false positive reaction. Low titres are more often associated with non-specific reactions. It is useful to test the serum by more than one technique preferably including a complement fixation test. If both complement fixation and flocculation tests are positive it is likely that the condition is syphilitic. This however should not convey to you that a serum, positive with multiple tests must be syphilitic. A positive complement fixation test associated with a negative flocculation test is likely to be false positive except in patients who have had prolonged anti-syphilitic treatment after acquired syphilis. The test may be duplicated in the same laboratory or may be done in more than one laboratory as no technician can claim absolute perfection in serological tests. The classical example of 14 per cent false results observed in the Copenhagen conference where only masters of the art, *i.e.*, author serologists were invited, should convince anybody of the inevitability of the false positive results in serological tests for syphilis.

Kahn verification tests may be done but they are not absolutely reliable. Neurath's euglobulin inhibition method should be tried if facilities are available.

REFERENCES

1. Dunner, L. and Mayer, R., quoted by Beerman, H.: Biologic False Positive Reactions to Syphilis, Am. J. M. Sc. **210** : 524-548, 1945.
2. Eagle, H.: On Specificity of Serologic Test for Syphilis, Am. J. Syph. Gonor. and Ven. Dis. **25** : 7-15, 1941.
3. Greene, R. A., Breazeale, E. L., and Andes, J. E., quoted by Beerman, H.: Am. J. M. Sc. **210** : 524-548, 1945.
4. Greval, S. D. S.: Lecinthinophile Eosinophilia and Error it may Cause in Cases of Tuberculosis and Asthma, Ind. Med. Gaz., **75** : 676-671, 1940.
5. Kahn, R. L.: Serologic Verification Test in Diagnosis of Latent Syphilis, Arch. Dermat. and Syph., **41** : 817-830, 1940.
6. Kahn, R. L.: Verification Test in Serology of Syphilis, J. Lab. and Clin. Med. **28** : 1175-1186, 1943.
7. Kolmer, J. A., *et al*: Studies on Role of S. pallida in Wassermann Reaction, Complement Fixation in Leprosy, Syphilis and Malaria with Spirochætal Antigens, Am. J. Syph. Gonor. and Ven. Dis. **25** : 300-318, 1941,

8. Moore, J. E., Eagle, H., and Mohr, C. F.: Biologic False Positive Tests for Syphilis, Suggested Method of Approach to their Clinical Study, J. A. M. A. **115**: 1602-1606, 1940.

9. Nelson, R. A., and Mayer, M. M.: J. Exper. Med. **89**: 369, 1949.

10. Neurath, H. *et al*: Biologic False Positive Reactions for Syphilis, Preparation and Properties of Serologically Active Globulin Fractions, Am. J. Syph. Gonor. and Ven. Dis., **31**: 347-373, 1947.

11. Pangborn, M. D.: New Serologically Active Phospholipid from Beef Heart Proc. Soc. Exper. Biol. and Med. **48**: 484-486, 1941.

12. Singh, B.: J. Indian Army Med. Corps. **3**: 186, 1947.

13. Singh, B.: False Positive Serologic, Reaction for Syphilis in Small-Pox Vaccinations, Ibid **82**: 609-610, 1947.

14. Singh, B.: False Positive Serologic Reactions for Syphilis in Eosinophilia, Ind. Med. Gaz. **83**: 77-78, 1948.

15. Singh, B.: False Positive Serologic Reactions for Syphilis in Leprosy, Brit. J. Ven. Dis. **25**: 159-169, 1949.

16. Stokes, J. H.: Modern Clinical Syphilology, W. B. Saunders Company, Philadelphia, 1945.

CHOLERA TOXIN ON RABBIT KIDNEY

S. N. De, J. K. Sarkar and B. P. Tribedi *

The pathology of cholera has not yet been properly understood, and some of the previous workers have not yet been able to explain the signs and symptoms. In this paper we wish to present part of our work on the general pathology of cholera toxin in the rabbit, a more complete account of which will be communicated later.

The second subculture of a recently isolated epidemic Inaba strain of *Vibrio choleræ* has been used to prepare the toxic material. A washed saline suspension of a twenty four hours' agar culture is prepared and diluted so that 1 c.mm. contains about 100 million organisms. The vibrios are killed by exposure to heat in a water bath at 56° C for 15 minutes. This preparation consists of the dead organisms and its toxic effects can be attributed to the endotoxin of the vibrios. Hence we have conveniently referred to the preparation as cholera toxin throughout.

An intraperitoneal injection of 1 c.c./Kg. of this suspension is found to be the minimum lethal dose for rabbits (weight = 1 to 1.5 Kg.) which regularly die in about two hours. There is a progressive fall of blood pressure until death. Hæmoconcentration as determind by measurement of hæmoglobin percentage, red cell count and packed cell volume of venous blood, is also progressive. These changes are shown in Table I and Fig. I.

TABLE 1 *Effect of intraperitoneal injection of minimum lethal dose of cholera toxin on blood and blood pressure of rabbit—average of 7 experiments Arrow indicates time of injection.*

	before	after			
	½ hour.	+½ hour.	+1 hour.	+1½hour.	+2 hours.
B. P. (mm. Hg.)	69	60	42	30	15
Hb. (per cent)	107	106	112	110	113
R.B.C. (millions/c.mm.)	7.2	..	8.4	..	8.1
P.C.V. (per cent.)	37	..	39	..	40

At autopsy the cut surface of the kidneys shows a very pale cortex and a vivid purple medulla. This appearance is very striking and is seen in six of the seven animals injected with the above dose. The reason for such gross appearance of the experimental kidney becomes obvious when we study thick frozen sections of the same, stained by Pickworth's method. This shows up only those blood vessels which contain blood and the vascular pattern is brought out like a beautiful

---

* Department of Pathology, Medical College, Calcutta.

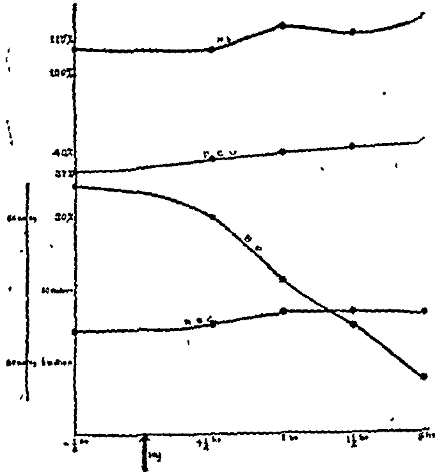


Fig. 1. Effect of I. P. injection of m.l.d. (1c.c.) of cholera endotoxin on blood and blood pressure of rabbit—average of 7 rabbit expts. Arrow indicates time of injection.

etching. Unfortunately the stain fades very soon. By this method it can be demonstrated that in the experimental kidneys there is an ischæmia of the cortical glomeruli and poor vascularity around the cortical tubules. This picture is constant and most marked in the most superficial cortex while deeper down it is variable. In its extreme form only the juxta-medullary glomeruli escape this ischæmia and from their efferents numerous pencils of prominent vessels are seen passing down the pyramids.

In thin sections, stained with hæmatoxylin and eosin, the congestion of the medulla is quite apparent and the limbs and loops of Henle situated here exhibit marked cloudy swelling of the epithelium while the collecting tubules are comparatively healthy. There is no evidence of casts, pigmented or nonpigmented, in the lumen. The juxta-medullary glomeruli in the boundary zone and the adjacent vessels are rich in red blood cells,—the Bowman's capsule and tubular lumina are widely open and the periglomerular convoluted tubules both proximal and distal, exhibit cloudy swelling. The main cortical glomeruli usually show the absence of red blood cells and so do the larger vessels. The capsular space and the tubular lumina in this situation are almost nonexistent suggesting absence of any urine in them. All the periglomerular tubules here, present a strikingly healthy appearance of the lining epithelium.

Thus we see that with one minimum lethal dose of the toxic preparation the blood laden with the toxin is more or less pervented from reaching the main cortical bed. So the cortical tubules appear healthy, and we also find evidence of absence of urine formation. On the other hand the congested medulla and the boundary zone have borne the brunt of the toxin diverted along with the blood from the cortex.

We have also tried the intraperitoneal injection of :—

(1) killed suspension of *V. choleræ*—sublethal dose (0.75 cc./Kg.)

(2) killed suspension of *V. choleræ*—heavy lethal dose (3.0 cc./Kg.)

(3) killed suspension of *B. typhosus*—sublethal dose (1 cc./Kg.) 1 c.mm. = 300 millions of bacteria)

(4) killed suspension of *B. typhosus*—heavy lethal dose (5 cc./Kg.) 1 c.mm. = 300 millions of bacteria).

(5) sterile normal saline (1cc./Kg.)

We have found that the cortical ischæmia and its escape from the effect of the toxin are found only with the first of these methods, namely, the injection of sublethal dose of cholera toxin. With the second, third and fourth methods, this mechanism has failed and the blood laden with the toxin has found a free passage to the cortex which therefore appears congested macroscopically, and under the microscope exhibits congestion of the glomeruli, which are packed with red blood cells, distension of Bowman's capsule and of tubular lumina and advanced cloudy swelling of the periglomerular convoluted tubules.

Thus with a moderate sublethal dose and with a minimum lethal dose of cholera toxin there is evidence of varying degrees of diversion of the renal blood flow from the cortex to the medulla. This appears to serve three purposes :—

(1) most of the cortical glomeruli are put out of commission, formation of urine is diminished, and further loss of body fluid is prevented.

(2) most of the toxin is diverted to the medulla, the vital glomeruli and the valuable periglomerular tubules get a chance to escape the action of the toxin and

(3) the ischæmic cortex is likely to produce V. E. M. (vaso-excitor material) and renin which tends to combat the fall of blood pressure—not always with success.

We have also seen that with a larger dose of cholera toxin, this mechanism fails and with typhoid toxin either in fatal or in sublethal doses, this mechanism does not come into play at all.

Study of kidneys from cases of human cholera in the light of these experimental findings will be very illuminating and is now being conducted by one of us in the Nilratan Sarkar Medical College, Calcutta. The cut surface of such a human kidney also presents a pale cortex and congested medulla and this appearance is strongly suggestive of the occurrence of the same shunting mechanism in such cases. It may be that in those cholera cases that recover after the stage of shock and oliguria, this protective mechanism has been successful. In those that lapse later into the stage of post-choleric uræmia, there has been irreversible toxic and/or ischæmic damage of the cortical parenchyma—either due to failure of this mechanism from a large amount of the toxin or due to too long a duration of the ischæmia.

HELMINTHIC ANTIGENS †

A short note on a new antigen

P. V. Gharpure *

There have been concentrated efforts on the study of immunological reactions in helminthic diseases. Antigens used have consisted of different stages in the life cycle of helminths—eggs, immature or mature eggs cultivated in the laboratory, developed embryos, larvæ at various stages of development and the adults. Tissues of hosts other than man have also been used. The use of adults for the preparation of antigen has been tackled in greater detail. The whole adult, different tissues without regard to their embryonic origin and tissues with identical embryonic origin, have been used as antigens for preparing anti-sera. A good deal of study has been aimed at immunological specificity of organs and tissues.

Canning[2] (1929) chose *Ascaris* on account of the simplicity of its structure. By preparing anti-sera in rabbits for different tissues of the *Ascaris*, Canning carried out precipitin reactions with his antigens. He concluded that the tissues of *Ascaris lumbricoides* are more or less specific.

The available literature on the immunological studies is so extensive as to need a good deal of space to review it. It is however worth noting that all antigens used have been derived from tissues either of the parasites or of the hosts or from cultural forms. If it is true that immunity reactions *in vitro* are possible so long as the parasite in the host is alive, the idea of using tissues of parasites as an antigen needs careful scrutiny. In most parasitic infections it is true that immunity reactions fail soon after the death of the parasite in the host. It is therefore not too speculative to presume that the antigen is elaborated by the parasite as a result of its metabolism. It is on these lines that this work was undertaken.

While studying the life of the *Ascaris* outside the body of the human host, the question of the possibility of an antigenic substance being elaborated by the parasites in the fluid medium was taken up. After using different types of fluid media, the simplest one consisting of sodium chloride solution, approximately 0.6 per cent was used. The fluid when used was in a sterile condition to start with. Adults with active movements were collected in the autopsy room and washed with tap water and finally with sterile saline and kept in a clear wide shallow jar in 0.6 per cent saline. The edge of the jar was vaselined and the lid slipped on.

---

† Paper read before the First Annual Meeting of the Indian Association of Pathologists on 25th November, 1950 at Agra.

* From the Pathology School, Grant Medical College, Bombay 8.

Selection of sexes was not done. The worms were watched and the very sluggish ones were discarded for fear of death and subsequent maceration. Maceration is bound to give off somatic substances comparable to tissue antigen.

The majority of worms survive over two weeks. Generally ten to twenty worms were kept at a time in a vessel 9" in diameter and 4" deep, the fluid used was not changed; 9-11 days were allowed and the worms removed. 25 c.c. of the fluid were collected in a glass capsule and allowed to evaporate. A thin layer of toluol was kept on the fluid. When the material was about to dry it was transferred to a agate mortar and rubbed. When all the fluid was lost in the process of rubbing, a few drops of ethyl alcohol were poured and ground again. Finally the material was suspended in 2.5 c.c. of sterile distilled water. It was this material that has been used for the detecting of an antigen.

Gould[3] (1945) suggested that a precipitin reaction is the most suitable one for the immunological study in relation to helminths. Boyd[1] (1947) favours the ring test.

The tests with the present material were carried out in capillaries about 1 m.m. in diameter and three inches long. Serum and the antigen were allowed to come in contact and the line of junction observed. First reading was done at the end of 30 minutes and final after four hours at room temperature. A milky ring was accepted as positive. Dilution of 1 in 5 to 1 in 160 were done. Six capillaries were used for each test.

The significant positive test was observed with the sera of parasitised hosts with 1 in 80 and rarely in 1 in 160 dilutions.

In control sera, occasionally, positive reactions were observed but not above 1 in 20 dilution.

This reaction, it is presumed, gave evidence that the worms during the extra corporal life were capable of elaborating a substance or substances antigenic in nature as determined, by *vitro* tests.

The object of this work is to throw light on the manner of the production of antigens by worms in the host. It is presumed that the helminths elaborate the antigens in and around their habitat. Taking the intestinal parasites, one should expect antigens in the contents of the bowel. These preliminary observations are reported as it is felt that in this communication there is a concept different to those put forth by previous workers.

Our definition of antigen is so changing as to make the work of studying substances alleged to be antigenic very much more complicated from a chemical point of view.

There are two matters which still require careful consideration—(*i*) possibility of eggs being discharged by the female. This would convert the antigen to an egg-embryo-larva-antigen. It is true some eggs do occur in the material. These can be removed by filtration and light centrifugalisation. It is impossible to presume an egg-free fluid unless one uses male worms only. (*ii*) The possibility of desquamated cuticle-tissue in the fluid. This is inevitable.

REFERENCES

1. Boyd, W. : Fundamentals of Immunity, p. 503 Inter-science Publication, New York, 1945.
2. Canning, A. : Precipitin Reactions with Various Tissues of Ascaris lumbricoides, and Related Helminths, Am. J. Hyg. **9**: 207-226, 1929.
3. Gould, S. E., : Trichinosis, p. 356 ; Charles, C. Thomas, Springfield, Illinois, U. S. A. 1945.

CURRENT MEDICAL LITERATURE

MEDICINE

SULPHONAMIDES AND ACUTE TONSILLITIS, a controlled experiment in a Royal Air Force Community, Macdonald, F.C., and Watson, I.H.: B.M.J. **1**: 323-326, 1951. 5 tables, 1 reference.

This experiment was begun with the very simple idea of attempting to find out whether sulphonamides were efficient and economically reasonable drugs to use in the treatment of acute throats, in particular under Service conditions. For the sake of convenience in control, the term acute throat was restricted to cases in which there was a frank inflammation of the tonsils. For this study 82 consecutive cases of acute tonsillitis were selected and divided into two equal parts in random manner. One-half of the cases were given 50 tablets, 0.5 Gm. each of sulphatriad and the other half received an equal number of lactose tablets identical in appearance to the former. All the patients were treated by rest in bed and given copious fluids to drink. Analysis of the clinical records revealed no difference between the controls and treated cases in the speed of recovery from various symptoms. However, the medical officer-in-charge was able to make an estimate of the goodness of cure which had a significant relationship to administration of sulphatriad. This experiment thus shows that the routine administration of sulphonamides to patients with acute throats cannot be supported by the results observed by these authors.

ERIC COELHO.

LYSIVANE AND ARTANE IN THE TREATMENT OF PARKINSONISM: Garai, O.: The Lancet, **1**: 429-432, 1951; 2 tables and 6 references.

The author has observed the comparative value of lysivane and artane in Parkinsonism; 51 cases received artane, 43 received lysivane and 24 had both compounds at different periods. All the patients were treated previously in most cases with the solanaceous group of drugs.

38 patients out of 51 who were treated with artane showed improvement; thus the improvement rate in the present series was 74.5 per cent. Post-encephalitic cases required and tolerated higher doses of artane; many cases required 60 to 100 mg. of artane daily though the average dose was 50 mg. a day. 31 of the patients treated with lysivane 150 mg. to 500 mg. daily showed some degree of improvement; the percentage of improvement in this series was 72. The improvement obtained with artane was somewhat greater than that with lysivane. Artane brought about a feeling of well-being which was potentiated by addition of amphetamine to many post-encephalitic cases. Most of 24 patients who received both lysivane and artane, preferred artane; even then a few were decidedly better with lysivane. Both artane and lysivane reduce the rigidity more than the tremor though the tremors do become less with these drugs. Both the drugs reduce the number and duration of oculogyric crisis. The present study group included idiopathic, post-encephalitic and arteriosclerotic types of Parkinsonism.

Lysivane is closely related chemically to phenergan and diparcol and all three drugs are phenothiazine derivatives; they block the transmission of impulses through the autonomic ganglia. Among the toxic effects of lysivane, giddiness, dryness of the mouth, depersonalization, nausea and vomiting were common and 9 of 24 patients who complained of these side effects had to discontinue the drug due to these unbearable side effects. Other side effects were blurred vision, increased rigidity, weakness of the legs, epigastric pain, drowsiness, increased tremor, slurred speech, ataxia and flushing of the face. Artane which is trihexyphenidyl and a piperdyl compound, is less antispasmodic, antisialogogic, mydriatic and cardio-vagal inhibitor than atropine. Though 19 patients complained of side effects of artane, in only 3 was it necessary to discontinue the treatment. The symptoms produced by artane were trivial and less severe than those seen with lysivane.

N. J. KOTHARI.

RADIO-ACTIVE IODINE IN THE TREATMENT OF HYPERTHYROIDISM: McCullagh, E.P. and Richards, C.E.: Arch. Int. Med. **87**: 4-16, 1951; 2 figs. 12 tables, and 6 references.

The authors treated 203 patients of toxic diffuse goiter and 78 patients of nodular goiter with I^{131}. The age range in the first group had been from 7 to 74 years while that in the latter group varied from 34 to 76 years. The treatment with I^{131} was selected usually because of old age, poor cardiac status, failure to maintain a remission after prophyl or methyl thiouracil therapy or aversion to surgical intervention. The diagnosis was based on clinical judgement, B.M.R., cholesterol determinations and I^{131} tracer uptake studies. The dose given initially was 4 millicuries for a gland of 30 Gm. and 1 millicurie for each additional 10 Gm. of the gland. The patients with toxic nodular gland required a much higher dose; the average total dose was 34 millicuries in this group. The patients were called after an interval of two months; if the B.M.R. was above 30 per cent half the initial dose of I^{131} was administered. Of the patients whose condition was in remission, 65 per cent required only one dose, 20 per cent two doses and only 7 per cent required 3, 4 or 5 doses. Only four of the 203 patients were known to have continued hyperthyroidism six or more months after the treatment was begun. The only complication observed in 19 patients was that of myxoedema. I^{131} had no effect in the prevention of exophthalmos. Out of 78 patients with nodular goitre, 18 or 23 per cent were still hyperthyroid; these patients were treated over a period of two to ten months with doses totalling as high as 68 millicuries; one patient who required 105 millicuries, was normal in 15 months. No case of hypothyroidism in a patient having toxic adenoma treated with radio active iodine, was observed.

N. J. KOTHARI.

THERAPY IN PSYCHOMOTOR EPILEPSY: Forster, F.M.; J.A.M.A., **145**: 211-215, 1951; 4 tables and 12 references.

In this article the author has given an idea of the comparative value of standard drugs like dilantin and phenobarbital and the recent drug phenyacetylurea (phenurone) in the treatment of psychomotor epilepsy. Psychomotor seizures are characterized by purposeful but irrelevant motor and/or psychic activity lasting from one to five or more minutes; they may occur in combinations with other types of seizures, and begin with upper gastrointestinal phenomena or uncinate fits. Gowers described such seizures as attacks of automatism following slight convulsions; according to Lennox *et al* they form a different entity; Jasper, Gibbs *et al.* by their E.E.G. studies have proved their focal discharge from the temporal lobe.

Nineteen patients with psychomotor attacks and associated grand mal and six with psychomotor attacks alone were treated by the author with dilantin, phenobarbital, mesantoin or with their combinations. 14 of 19 and 3 out of 6 in the above mentioned group improved with the standard therapy. The age of onset had no effect on the therapeutic results. 10 patients had the duration of disease for less than 10 years and 15 had it for more than 10 years; 8 improved in the first instance and 9 in the latter instance.

Out of 27 patients treated with phenyacetylurea, 8 were free from seizures or nearly so with the standard drugs administered previously; 13 out of 19 patients who received phenyacetylurea 1.5 to 3.5 Gm. a day, became seizure free but four manifested so severe a depression as to discontinue the drug. In all, 9 out of 19 were seizure-free and without any side effects like depression, anorexia, vomiting, and hæmatemesis. The age of onset, the duration of the disorder and the multiplicity of seizures bore no relation to therapy.

In one patient temporal lobotomy and in four, excision of the tip of the the left temporal lobe under the control of E.E.G. were performed. The surgical procedure resulted in complete relief in only one case; the other cases had temporary relief and the drug therapy had to be continued later on to control the seizures.

N. J. KOTHARI.

GARGLES, Mathers, R. P. The Pract. **166**: 293-295, 1951

The author on enquiring among general practitioners as to their use of gargles, learned that most of them use one form of gargle for all conditions. In this article he outlines the value of gargles.

A gargle is an aqueous solution intended for use as a prophylactic or in treatment of an affection of the throat. Prophylactic gargles are no longer prescribed now as their antiseptic value is very slight, if any; it does not penetrate the crypts of the tonsils nor does it reach the lateral or posterior walls or the lower part of the pharynx. Alkaline gargles are used to dissolve and clear away the thick mucus, soothe the throat in acute pharyngitis and acute tonsillitis. The gargles should be used as hot as can be tolerated. The simplest form of an alkaline gargle is plain sodium bicarbonate, a teaspoonful in a tumbler of hot water. Glycothymoline (the compound of glycerine of thymol B.P.C.) diluted in water makes a pleasant form of alkaline gargle. Antiseptic gargles which have a deodorizing action are of great value in the treatment of sloughing conditions like malignant disease of the pharynx or fauces occurring after radiotherapy or diathermy. Potassium permanganate 2 gr. in 10 ounces of water forms harmless compounds with foul smelling gases and liquids and acts as an efficient deodorizer. 1 oz. of glycerine of carbolic acid diluted in 20 ounces of water is likewise beneficial. Free chlorine is sometimes used for its deodorizing action. The prescription is as follows:

Potassium chlorate	gr.	200
Hydrochloric acid	gr.	40
Distilled water	oz.	20

Dilute with equal parts of water.

The use of astringent gargles to shrink the elongated uvula has fallen into disuse since it is now known that the underlying cause is an irritative or allergic condition. The astringent drugs in common use are alum and tannic acid. The glycerine of either in the strength of 1 to 8 ounces of water makes a useful gargle. Both drugs may be prescribed.

Alum	gr.	60
Tannic acid	gr.	80
Distilled water to	oz.	10

A desertspoonful diluted with water.

A gargle used for syphilitic lesions of the mouth and pharynx, was a mixture of potassium chlorate, 80 gr., in black lotion, 8 ounces. This was diluted with equal parts of water.

ERIC COELHO.

TUBERCULOUS MENINGITIS, RESULTS OF TREATMENT WITH STREPTOMYCIN AND INTRATHECAL SULPHETRONE, Calnan, W.L. and Rubie, J.: B.M.J. **1**: 792-793, 1951.

The authors report a controlled trial of intrathecal sulphetrone in addition to streptomycin for tuberculous meningitis. The dose of sulphetrone administered intrathecally was 200 mg. daily. The toxic effects encountered were convulsions in 5 cases, excessive head retraction and opisthotonos in 7 cases, mental symptoms in 3 cases and cyanosis in 1 case. In 5 patients the reactions were so severe as to necessitate an interruption of treatment. Observation for a minimum of 12 months showed a survival rate of 58 per cent which was the same as in the control group. The authors came to the conclusion that sulphetrone when injected intrathecally in combination with streptomycin treatment, was of no value in the treatment of tuberculous meningitis.

ERIC COELHO.

HORMONES OF THE SYMPATHETIC NERVOUS SYSTEM AND THE ADRENAL MEDULLA, Von Euler, U.S.: B.M.J. **1**: 105-108, 1951; 1 table, and 42 references.

Elliot in 1905 put forward the hypothesis of neurohumoral transmission of nerve impulses, which was proved in 1921 when an adrenaline-like substance was isolated by Loewi, Cannon and Uridil on stimulation of sympathetic nerves. However a stimulation of sympathetic nerves produced inhibitory and excitatory actions, which necessitated the assumption of two different active substances sympathin I and E. It was pointed out by Barger and Dale in 1911 that the non-methylated ethanolamino base, nor-adrenaline might be responsible for excitatory reactions and he proved in 1947 that the substance liberated on sympathetic nerve stimulation was nor-adrenaline.

Nor-adrenaline is formed by the action of a decarbolating enzyme on dihydroxyphenylalanine; the intermediary product is hydroxytyramine. It shows greater resistance to oxidation than the adrenaline; it is inactivated by an amine oxidase and a catechol oxidase and is excreted in the urine partly in the pure form. It is held by some that nor-adrenaline is the precursor of adrenaline but the reflex vascular effects produced by nor-adrenaline rule out such a view. Nor-adrenaline is distributed in every organ having adrenergic nerve fibres; it is the dominating adrenergic hormone; it is present in small amounts in venous blood of man and animals. Both nor-adrenaline and adrenaline are found in the adrenal extracts but the relative amount of these two vary in different species and in the same individual at different times. Nor-adrenaline and adrenaline can be estimated by biological or by colorimetric methods.

Nor-adrenaline has weaker inhibitory effect on the smooth muscle than that of adrenaline but on contracting uterus nor-adrenaline is more active than adrenaline. Adrenaline causes rise in systolic pressure and vasodilatation with the resulting increase in the minute volume while nor-adrenaline causes a parallel rise in systolic and diastolic pressure, bradycardia and vasoconstriction leaving the minute volume of the heart unchanged. Coronary arteries and intestinal vessels have vaso-dilating effect with nor-adrenaline. Nor-adrenaline has smaller vasoconstrictor action on the renal blood flow than adrenaline. Thus many features of the hypertension are consistent with an action of nor-adrenaline. The calorigenic action of nor-adrenaline is less than that of adrenaline which naturally is more glycaemic in its action and more active in the formation of lactic acid. Adrenaline is six times more active than nor-adrenaline in liberation of cortical hormones. Adrenaline causes anxiety, irritation and discomfort, none of which are caused by nor-adrenaline. Thus nor-adrenaline is less toxic and better suited for combating low-blood pressure due to shock; it may be administered with advantage as an infusion. Nor-adrenaline is the sympathetic neuro-ergone for general service while adrenaline acts as an adjuvant for more special purposes like metabolic actions.

N. J. KOTHARI.

PSYCHO-PHYSIOLOGIC RELATIONSHIPS OF ASTHMA AND URTICARIA TO MENTAL ILLNESS: Funtenstein, D.H.: Psycho-Somatic Medicine, **12**: 377-385 1950; 7 figures and 31 references.

The first to draw the attention to the effect of emotion on asthmatic attacks was Hippocrates. The importance of emotional factor in asthma has been stressed by various workers of psychosomatic medicine; a number of cases have been reported in which a mental illness was substituted for asthma; the low incidence of asthma in mental institutions has been well known; the patients suffering from psychosis or anxiety state are free from the attacks of asthma during their psychotic phase. Because of this intriguing relationship between asthma and psychosis, the author carried out tests on 7 patients with asthma and one patient with urticaria, to ascertain changes if any in their autonomic nervous system during the psychotic phase. After complete physical and mental examination, on the first day 1 cc. of normal saline was injected intravenously; on the second day 0.05 mg. epinephrine hydrochloride dissolved in 0.5 cc. of distilled water was administered intravenously; on the third day 10 mg. of mecholyl was injected intramuscularly, the blood pressure readings were taken frequently and followed till it returned to normal. Three patients who were in psychotic phase of their illness showed marked increase in the sympathetic nervous system activity and the recovery from the effect of mecholyl was rapid; the asthmatic attack precipitated by mecholyl was of a short duration and mild in nature. When these patients were in their non-psychotic phase the effects of mecholyl were not easily overcome; the asthmatic attack was of severe intensity and sustained. In the fourth patient the results were similar to those observed above except that there was elevated blood pressure during the psychotic phase of his illness. In the remaining two cases, the results with the mecholyl test were similar to those observed above but with the epinephrine injection there was precipitation of anxiety which was increased with electro-convulsive therapy.

The same tests were conducted in one patient suffering from urticaria. When the patient was free from the psychotic phase, the effects of injection of mecholyl were quickly overcome but during the psychotic phase "cholinergic urticaria' induced by mecholyl could not be easily overcome. Whenever the patient exhibited paranoid activity or anxiety state, the attacks of urticaria were precipitated; the same phenomenon happened by exposure to heat and cold or on administration of mecholyl. Thus the emotional problem has a bearing on the release of acetylcholine from cholinergic nerve fibres, which leads to the formation of urticaria.

N. J. KOTHARI.

COMPARATIVE RESULTS IN SEIZURE CONTROL USING PHENOBARBITAL, DILANTIN AND MESANTOIN: Ruskin D. B., The American Journal of Psychiatry, **107**: 415-421, 1950; 4 figures and 1 table.

The author studied the effects of phenobarbitone, dilantin and mesantoin on 53 patients, with a total of 3015 seizures for the year 1947. The group was divided into three parts, 18 into two subgroups and 17 into third; the subgrouping was based on successfully balancing individual seizure records of individuals and subgroups. 19 patients experienced toxic reactions from mesantoin; 9 patients had toxic reactions from dilantin and in only 5 of the 17 patients was there a reaction to both mesantoin and dilantin taken together; 3 patients tolerated the drug separately but experienced toxic reaction when mesantoin and dilantin were given in combination. No patient who received phenobarbitone experienced any toxic reaction. Phenobarbitone was the final drug of choice for as many as the total number of patients receiving either dilantin or mesantoin. The percentage of patients controlled by phenobarbital or dilantin and penobarbital combination was 65 per cent; by adding mesantoin as a supplement to phenobarbital the percentage was increased to 75 per cent of the total group, leaving only 25 per cent of the patients controlled by dilantin alone, mesantoin alone and a combination of phenobarbitone, dilantin and mesantoin. All the three drugs used in combination or individually resulted in improvement of 49 of the total 53 patients. The effective anticonvulsant action of mesantoin when used alone was double that of dilantin while it was one-fifth of dilantin-phenobarbitone combination when mesantoin-phenobarbitone combination was used. Mesantoin in this study proved twice as toxic as dilantin. The conclusion from the present study leads us to phenobarbitone as effective an anticonvulsant drug as mesantoin and dilantin and with hardly any toxic effects which are so common with the latter two drugs, which may be used as supplementary or only occasionally as substitute drugs to phenobarbital therapy. In the discussion Dr. Doolittle recommends phenobarbital and ½ gr. caffeine combination, particularly in petit-mal manifestations along with grand-mal seizures.

N. J. KOTHARI.

LIQUEFACTION OF EXUDATES: The Lancet, **2**: 807-808, 1950, 12 references.

Various drugs have been tried in the liquefaction of exudates. Streptokinase and streptodornase, enzymes derived from streptococci A, have been experimented with by Tillet and colleagues, cruder preparations of these enzymes by Cathie, desoxyribonuclease from the pancrease of the ox by Armstrong and White, a detergent to a solution of antibiotic by Grace and Bryson, and finally trypsin by Reiser and his colleagues. Streptokinase and streptodornase have a fibrolytic activity and cause the disappearance of extracellular desoxyribonucleic acid and degenerating cell nuclei from purulent exudates, without interfering with the activities of living leucocytes. Cathie obtained excellent results in patients with tubercular meningitis by using streptomycin with crude preparations of streptococcal enzymes. Desoxyribonuclease *in vitro* is highly active and liquefies the fibrils in the sputum. It has no toxic action when injected intrapleurally or intrathecally. When a solution of penicillin containing 10,000 units—20,000 units per c.c. with 0.1 per cent of a detergent, is instilled locally for four to ten days, the detergent causes disintegration of pus, blood clot and other debris and its action is like that of desoxyribonuclease. The detergent may have an irritant effect locally. The use of highly, purified trypsin has been reported from the Armour Laboratories. The tuberculous empyema cavity washed out with a solution of trypsin daily for seven to ten days, removes all the debris and leaves the cavity clean and sterile. It is hoped that with the discovery of these new liquefying agents, the problem of fibrosis and adhesions would be solved ; antibiotics will have assess to many organisms which are usually walled off by the fibrin formation. These enzymes are antigenic and may give rise to sensitization. Removal of fibrin in an immediate post-operative period has the danger of hæmorrhage.

N. J. KOTHARI

SURGERY

EXPERIENCE WITH POSTOPERATIVE TEMPERATURES ABOVE 108°F. Mangiardi J., Am. Jour. Surg. **81** : 189-191, 1951.

Patients can survive temperatures above 108°F with full recovery *if* properly treated. Experimental work shows that living tissue does not become irreversibly damaged until the temperature reaches 115°F. The author tries to show that if these patients can be tided over the temperature crisis, they will have more time to combat diseases and a certain number would survive who would otherwise be lost.

In extreme hyperpyrexia there is a markedly raised basal metabolic rate, + 50 to + 75 in severe cases. Such a sudden increase in metabolism puts a severe strain on the resources of the body. Oxygen is supplied with difficulty for it has been shown that the oxygen tension of arterial b'ood is materially reduced in cases of high fever. The pulse is increased to 5 to 10 beats per minute for each degree rise in temperature (F). Later the pulse rate is so rapid that cardiac output falls, and so does the blood pressure. Blood volume diminishes due to water loss by skin and lungs, this leads to hæmoconcentration and peripheral failure. Progressive dehydration and high metabolic rate increases the body temperature and constitutes a *vicious circle. The ganglion cells of the central nervous system shrink.* There is early rise of blood sugar due to release of sugar from the liver with hypersecretion of insulin and adrenaline. The liver function becomes deficient as a result of the hyperpyrexia itself and jaundice and liver failure has been noted following hyperpyrexia. When the liver is depleted of glycogen, disaster is at hand; proteins and fats are burned up and ketonuria occurs. Death finally occurs due to failure to supply the colossal demands for oxygen fuel and water together with profound changes in blood chemistry and blood volume.

In combating these ill effects two principles must be kept in view. 1. reduction of the temperature 2. keeping the patient alive while the temperature is being reduced.

Reduction of temperature—Augment the loss of heat from the skin by moistening the body and allowing fans to play upon the body. Ice is placed in the axillæ, groins, and neck over the large blood vessels in an attempt to cool the circulating blood. This is continued until the temperature drops to 102°F ; thereafter no positive effort is made to reduce the fever since these patients stand sudden changes of temperature poorly and the change may be irreversible.

Keeping the patient alive—Nasal oxygen is administered, water and isotonic saline is given, the amount and rate depending upon the individual case. In addition the author has used continuous intravenous infusions of 50 per cent glucose in distilled water for the duration of the temperature crisis to supply large amounts of glucose as quickly as possible as fuel and to spare depletion of the liver. Repeated intravenous injections of 50 per cent glucose are not as satisfactory as continuous, as much of the sugar is excreted by the kidneys without being used andfurther increasing the dehydration. The author believes that continuous infusion of 50 per cent glucose given rapidly accounted in large measure for the successes reported by him, He reports 3 cases in which this treatment was used. In the first case there was a severe postoperative thyroid crisis in a woman of forty-four years. The temperature was over 110°F and pulse rate over 160 per minute and the patient was comatose. The above treatment was given with continuous infusion of 600 cc. of 50 percent glucose. The temperature remained unrecordable for one hour and then suddenly dropped to 107°F. After 3 hours it was 103°F and after four hours it was 100°F. The patient recovered and was discharged on the eleventh postoperative day quite well.

The second case was that of a girl with peritonitis after an appendicular perforation. In spite of penicillin and streptomycin and drainage the temperature shot up to over 110°F the patient became comatose and the pulse and blood pressure were unrecordable. The above treatment was given with 250 cc. of 50 per cent glucose. After 30 minutes the tempeature was 109°F per rectum, after one hour 106°F and after four hours 99°F. A stormy pcstoperative course ensued, but the patient made an eventual recovery. This case proves the point that given a chance to survive the temperature crisis, the patient is given time to fight the underlying disease.

E. J. BORGES.

CARDIAC ARREST, Anderson, R.M., Schoch, W.G. and Faxon, H.H.: New England Journal of Medicine, **243**: 905-908, 1950.

The authors record a case of cardiac arrest during operation which was saved by cardiac massage. Within the last decade several such cases have been recorded. Few patients can survive the anoxia of the brain produced by more than three minutes of cardiac standstill. It is necessary therefore that the anæsthetist must recognise or suspect the condition and notify the surgeon. It should be emphasised that cardiac massage from below the intact diaphragm against the chest wall is far less efficient than grasping the heart either through an opening in the diaphragm or in the chest wall and compressing it between the thumb and the fingers. The rate of compression should be at least sixty times a minute to achieve the most efficient blood flow. A small emergency kit of instruments to open the abdomen or thorax should always be present and plainly marked in a central position in the operating room in the event that no other instruments are available when circulatory arrest occurs. Electrical equipment for serial defibrillation should be ready if possible. It is also recommended that a syringe containing 9.5 cc. of procaine in a 1 per cent solution and 0.5 cc. of epinephrine (1 : 1000) should always be available in a central location for intravenous or intracardiac injection.

Case Report. G.L.M.retired 78 year old clerk was admitted to the hospital for the first time on May 4, 1949 with symptoms and signs strongly suggestive of a stone in the region of the gall-bladder. The patient had a blood pressure of 190/80 and also gave a history of a cardio-vascular accident 5 years before the present illness. The diagnosis of a cardiac consultant with regard to the heart condition was : hypertensive heart disease with a systolic murmur possibly due to dilatation of the aorta or aortic stenosis. The electrocardiogram showed marked left ventricular hypertrophy and strain. The patient, in his opinion, was not a very good operative risk, but at best he was not in cardiac failure. The patient underwent an operation of cholecystectomy and choledochostomy. He withstood the operation well. 48 hours after operation, the patient was found with cold clammy skin and complaining of burning pain under the manubrium. The heart rate was irregular suggesting fibrillation. The electrocardiogram was suggestive of anterior infarction. He was treated with digitalis and quinidine. Slight abdominal distension was first noted on the fifth post-operative day and fluctuated considerably in degrees for the next few days. On clinical and roentgen examination, a diagnosis of small bowel obstruction was made. Re-exploration of the abdomen was done eleven days after the first operation under endotracheal ether anæsthesia. When the abdomen was opened, the omentum was found adherent to the bed of the gall bladder with fairly dense adhesions. The surgeon had just begun to free the adhesions, when suddenly the anæsthetist noticed that the blood pressure was not obtainable. This was half an hour after the operation was started. The surgeon was asked to feel for aortic pulsation and he found that none was present. He was encouraged to open the left leaf of the diaphragm. The heart was found pulseless and flabby and the surgeon began to squeeze the heart an estimated stroke of 60 per minute. During this time an intravenous injection of 9.5 cc. of procaine in 1 per cent solution and 0.5 cc. of epinephrine (1 : 1000) was given through a 3-way stopcock in the tubing and pumped along by refilling the same syringe from the infusion bottle. Within 30 seconds of the time that cardiac massage was started there was an occasional spontaneous contraction of the ventricles, between the artificial strokes and about one minute later regular spontaneous rhythm was resumed. Within 30 seconds of the beginning of spontaneous cardiac action, the pulse could be obtained at 80, and the blood pressure at 240/110. Shortly after the appearance of the pulse and blood pressure, spontaneous respirations were obtained at 20 per minute. The respirations had all this time been maintained by artificial contraction of the breathing bag. Since the obstruction of the small bowel was almost complete, it was considered advisable to continue the operation. There was a fall in blood pressure during the course of the operation, and this was combated with the subcutaneous injection of 3 minims of Neo-synephrin in 1 per cent solution. Electrocardiographic studies were also made in all the leads. At the end of the operation, the patient's colour was good and the anæsthesia had lightened to such an extent that the patient was swallowing. The patient was fully conscious and talking two hours after the end of the operation. There was no evidence that his mental processes were any different than they had been pre-operatively. Recovery from this operation in other respects was also uneventful.

B. G. FARIA.

PEDIATRICS

IMMUNIZATION PROCEDURES IN INFANCY, Miller, J.J., Postgraduate Medicine **9**: 160-163, 1951.

Combined immunization of infants against diphtheria, pertussis, and tetanus has been simplified due to three factors ; (1) enhancement of antigenicity of toxoids and vaccines by adjuvants like alum, aluminum hydroxide, and aluminum phosphate ; (2) purification and concentration of toxoids, and (3) employment of mixtures of both toxoids with *Hemophilus pertussis* vaccine. Precipitated or adsorbed toxoid vaccines result in superior immunity when compared with 'fluid' (neither adsorbed nor precipitated) mixtures ; with the latter however, immunization is accomplished more rapidly.

With precipitated or adsorbed toxoid vaccine for routine immunization, three injections of 0.5 cc. each at intervals of not less than a month are recommended ; longer intervals though permissble delay the attainment of immunity against pertussis though it may finally result in higher diphtheria and tetanus antitoxin levels. The total number of killed *H. pertussis* recommended is 40,000 million. When rapid primary immunization against pertussis and/or diphtheria is required, "fluid" triple antigen should be used ; three injections at intervals of two to four weeks are given, the dose depending on the manufacturer's instructions. In this case the total dose of *H. pertussis* should not be less than 80,000 million.

In the author's opinion, immunization should start at the third month, with the first recall (or 'booster'') injection one year after completion of the course; should immunization be started after the 6th month, the first recall can be given two years after the course has been completed; the dose at these recall injections should be 0.5 cc. of the precipitated or adsorbed mixture. Thereafter recall injections are necessary every 3 years, smaller doses being safely used. The author discontinues the use of the mixed antigen when the child reaches the age of 10 to 12 years as reactions to the diphtheria toxoid component are severe: triennial injections of tetanus toxoid are however continued. Intimate exposure to a case of tetanus, diphtheria or pertussis is an indication for an emergency 'booster' of the respective vaccine, the 'fluid' product being preferred; 10,000 million *H. pertussis* is recommended if the exposure occurs a year after the last combined antigen, the doses of the other two depend on the manufacturer's instructions.

A few precautions are mentioned. Only well babies and well children should be injected. The injection must not be given in the presence of any illness or in a child with known cerebral damage. Asthmatic children and children with histories of febrile convulsions should be given at first a fractional dose. The volume of the second injection is decreased by 0.1 cc. if somnolence occurred after the first; fever is treated by aspirin after the injection. During epidemics of poliomyelitis all injections are postponed.

The author recommends primary smallpox vaccination any time during the first year. The vaccine should be stored at a temperature below 32°F at all times, failure to do so decreases the likelihood of a 'take.'[3]

F. A. Nazareth.

NOTIFICATION

Raptakos Medical Research Board

AWARD OF FELLOWSHIPS.

The Raptakos Medical Research Board will consider applications for the award of Fellowships for research work in recognized institutions on Medical and Allied subjects.

The awards normally consist of Rs. 3,000 per year for a Fellowship and Rs. 750 per year towards special equipment or chemicals.

Applications should be forwarded through the guides, under whom research work will be carried out, and the Head of the Institution.

The applications should be accompanied by six copies of a brief statement of the research project and the comments of the guide regarding the suitability of the project and the facilities existing at the Institution.

Fellows appointed should have an M.B.B.S., or M.Sc., degree or its equivalent or not less than 2 years' experience in research work after B.Sc. The awards are made annually and may be renewed on the basis of satisfactory progress.

Applications for Grants for the year commencing 1st January, 1952, should reach the Secretary, Raptakos Medical Research Board, C/o Raptakos, Brett & Co., Ltd., Dr. Annie Besant Road, Worli, Bombay—18, before 1st September, 1951.

NOTICE TO CONTRIBUTORS

THE INDIAN JOURNAL OF MEDICAL SCIENCES which appears monthly, publishes original articles in all branches of medicine and allied sciences, case reports, progress reviews, book reviews, summary of current medical literature and author's summaries. Papers submitted for publication and all editorial communications should be addressed to the Editor, Indian Journal of Medical Sciences, Back Bay View, New Queen's Road, Bombay 4.

Papers submitted for the JOURNAL are accepted on the understanding that they have not been and will not be published in whole or in part in any other journal; they are subject to editorial revision.

MANUSCRIPTS should be in double-spaced typing on one side on quarto or foolscap sheets with a margin of not less than 2 inches. They should bear the name and full address of the author to whom proofs are to be sent. A paper should conclude with a brief summary giving in numbered paragraphs the results and conclusions described in the paper; it should not exceed 1/20th of the length of the paper.

TABLES.—Tables should be typed on separate numbered sheets and referred to the text by Arabic numerals.

ILLUSTRATIONS.—Illustrations will not be accepted unless they reach a certain standard of excellence technically, present an attractive appearance and add significantly to the value of the presentation. They are to be referred to in the text by Roman numerals. Legends or captions are to be typed on separate sheets and numbered correspondingly. Line drawings and graphs, which should be about twice their intended final size, are to be carefully drawn in Indian ink on tracing linen, or card board, or stout smooth white paper; blue-lined graph paper of good quality may be used for graphs. Lettering of drawings and graphs must be lightly written in pencil. When half-tone reproduction of X-ray or other illustrations is required the author is advised to send the original film unless he wishes to bring out special points in a print of his own choice. Photographs and photo-micrographs should be printed on glossy paper, should be larger than the size desired for reproduction, and if transmitted through the post in a tube, should be rolled with the picture outside.

REFERENCES.—At the end of the paper references should be arranged in the alphabetical order of the author's names and should include: author's name, followed by initials; the name of the article, name of journal, volume underlined; pages, and the year. References made to books should include the author's name followed by the title underlined, pages, town of origin, the publisher and the year.

Examples. 1. Coller, F. A., and Maddock, W. G.; The Function of Peripheral Vasoconstriction, Ann. Surg. **100** : 983-992, 1934.

2. White, J. C., and Smithwick, R. H.: The Autonomic Nervous System, pp. 271, New York, the Macmillian Company, 1941.

Citations in the text should be by the author's name followed by the number listed in the reference.

PROOFS.—Contributors will receive one proof in galley, but it will be assumed that all but verbal corrections have been made in the original manuscript.

REPRINTS.—25 reprints of an article will be given to the author or divided among the authors. Additional reprints can be supplied at cost price if application is made when the proofs are returned.

COPYRIGHT.—Papers which have been published become the property of the Journal and permission to republish must be obtained from the Editor.

Indian Journal of Medical Sciences

(INCORPORATING THE MEDICAL BULLETIN)

VOLUME 5 AUGUST 1951 NUMBER 8

COPYRIGHT BY THE INDIAN JOURNAL OF MEDICAL SCIENCES

THE PROBABLE ROLE OF THE HILSA FISH, HILSA ILISHA (HAM) IN MAINTAINING CHOLERA ENDEMICITY IN INDIA

C. G. Pandit * **and Sundar Lal Hora** †

INTRODUCTION

The study of factor or factors governing the endemicity of cholera in India has engaged the attention of Indian workers for many years. Attempts were directed to provide answers to two main questions, namely, (1) where does the infection persist in the inter-epidemic periods, and (2) does the cholera vibrio live quietly in tanks or other water only to assume pathogenicity under favourable conditions, or does it maintain itself in the individual, producing perhaps, a mild gastro-intestinal upset which goes unnoticed? Do such sub-clinical infections constitute a link between two outbreaks of cholera, say, in a village?

It may be profitable to summarize the results of investigations which had been undertaken in recent years. As regards the "carrier state," either in convalescents or healthy contacts, the evidence available so far goes to show that it is of a very short duration, especially so in healthy contacts. Examinations of water-sources, *e.g.*, tanks, canals and rivers, have shown that the presence of cholera vibrios is noted in these, only in the presence of an epidemic of cholera in the vicinity and not otherwise. During inter-epidemic periods, therefore, it would appear that with the techniques at present available for investigation, cholera vibrios cannot be demonstrated in the environment of the population. The recent work in the Cauvery Delta has not provided, so far, any evidence that sub-clinical infection exists in the population during inter-epidemic periods.

It is customary to prepare a forecast of cholera incidence for the ensuing year on the basis of the available data of the past 25 years or more. Such a forecast also brings out the chronological order of the spread of the disease in the areas concerned. The forecasts are, to a certain extent, valid because they are based on the general trends of cholera mortality during those years. However, in view of the changed socio-economic conditions and acceleration in the modes of transport during the past several decades, as well as the activities of the Public Health Departments during recent years, including attempts at large scale immunisations, it would be logical to assume that the overall cholera picture should have altered to some extent at least, particularly in respect of the chronology of the epidemics. This has not happened. The basic factors, therefore, which would contribute towards the maintenance of endemicity in an area have remained obscure so far.

---

* Secretary, Indian Council of Medical Research, New Delhi.

† Director, Zoological Survey of India, Calcutta.

As stated by Taylor [5] (1940), the problem of primary importance in the epidemiology of cholera is the existence of areas in which cholera is permanently present. The status of several areas in the country from the point of view of their endemicity has recently been investigated by Swaroop (in manuscript) and certain areas, which can be regarded as truly endemic, have now been demarcated. This study, however has not added materially to our knowledge concerning the factors governing endemicity. In view of the results recorded above, it would appear to be necessary to look for other reservoirs of infection besides water-sources and human population. The question was fully discussed by the joint OIHP/WHO Study Group in Cholera during their third session in New Delhi. The Group made the following recommendations :—" Following the Japanese work on infected fish and dissemination of cholera through that source, and in view of the possibility that fish infected with cholera vibrios could infect water supplies, further investigations on the role of fish and other aquatic fauna and their potential danger in infecting water supplies should be made."

It was this directive that brought the two authors of this note together in Calcutta for a preliminary discussion of the problem in all its aspects. Dr. S. Swaroop, Professor of Statistics, All-India Institute of Hygiene and Public Health, Calcutta, was also present at the preliminary discussion. The data collected by Dr. Swaroop was examined in detail. The study of the map of endemicity of cholera in India, reproduced here, (Fig. 1) showing the river systems and the degree of endemicity based on the average incidence of 45 years of lowest cholera mortality during the period 1901–1945, clearly showed that if any one fish could be regarded as the " reservoir of infection " it could be the Hilsa fish, map of whose fishery in India is given here (Fig. 2) for comparison with Swaroop's map of the endemicity of cholera in India referred to above. In our general discussion the known facts concerning the cholera endemicity in India and the present state of knowledge concerning the Hilsa fisheries in India were briefly reviewed. It was, indeed, interesting to note that during this, as well as in our subsequent

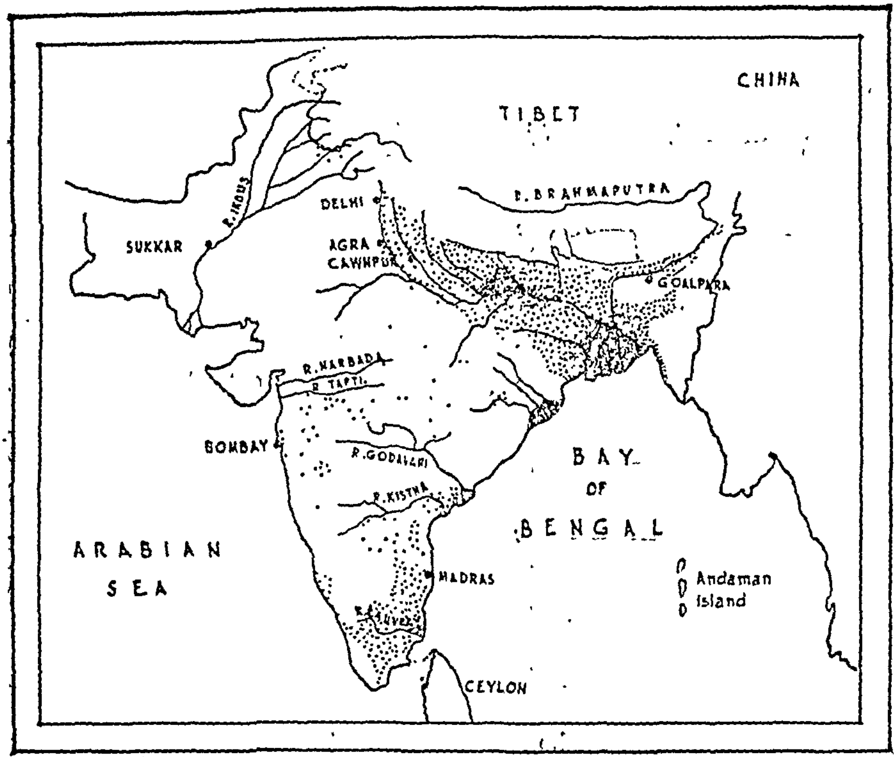


Fig. 1. Degree of endemicity of lowest cholera mortality (1901 to 1945)

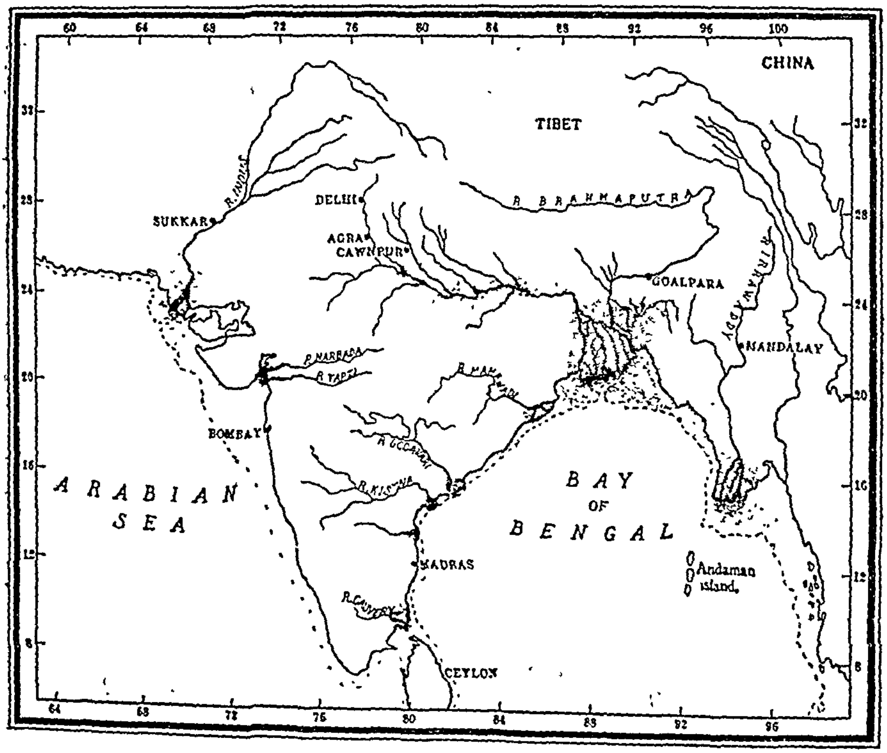


Fig. 2. Distribution and intensity of Hilse fishery along rivers and coasts

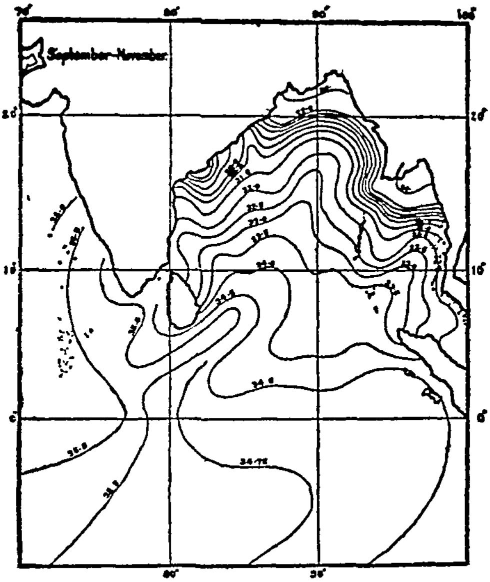


Fig. 3. The surface salinity of the Bay of Bengal (Sept.-Nov.)

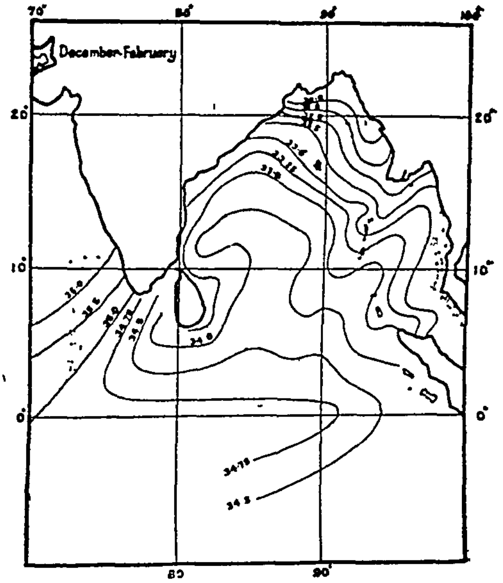


Fig. 4. The surface salinity of the Bay of Bengal (Dec.-Feb.)

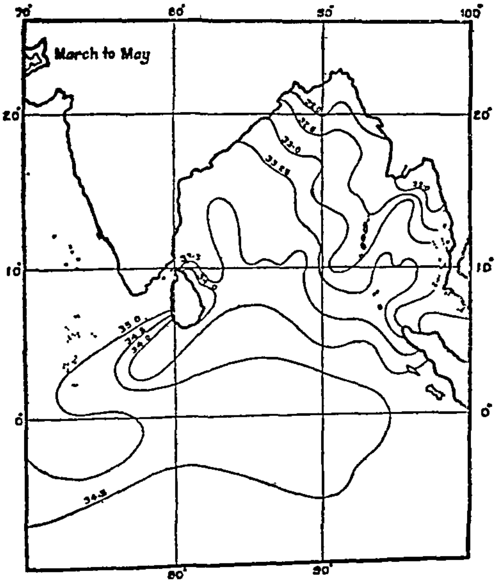


Fig. 5. The surface salinity of the Bay of Bengal (Mar.-May)

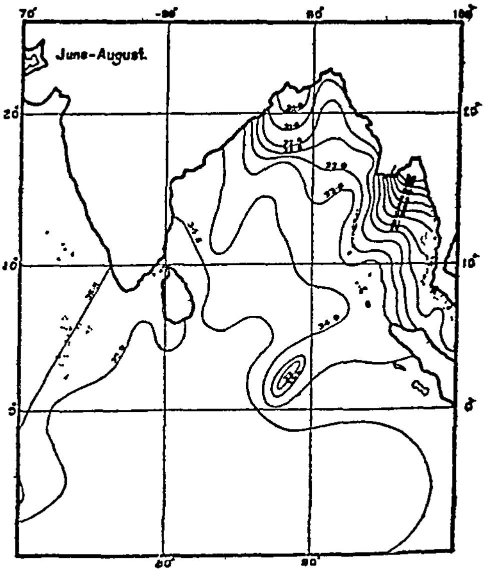


Fig. 6. The surface salinity of the Bay of Bengal (Jan.-Aug.)

discussions, some of the major characteristics relating to the prevalence of cholera in India in endemic areas could be explained fairly closely, with the knowledge so far available, though meagre, regarding the ecology and life history of Hilsa. It appears to us that such a close correlation could not be a mere coincidence. This discussion, therefore, brought out the necessity of investigating the probability of Hilsa fish as a "reservoir of infection" for the cholera vibrio. In the following account we set forth the observations which have led us to the conclusion stated above.

CHOLERA ENDEMICITY AND HILSA FISHERY

From the reading of the map prepared by Swaroop on the endemicity of cholera, the following important points emerge for consideration :—

1. There are distinct areas of high endemicity in India which are separated from one another and are located in the deltaic regions of the rivers falling into the Bay of Bengal ;
2. The extent of each such area is correlated with the size of the delta and therefore, the main focus lies in the very extensive Ganges-Brahmaputra delta ;
3. The inland focus lies along the Ganges in Bihar and United Provinces where the large Himalayan rivers, such as the Kosi, the Gandak, the Sone, the Gogra, and the Gomti, join the Ganges river and at their mouths fan out in deltaic formation ;
4. The estuaries of the three rivers of Orissa, namely, the Barabalang, the Svarnrekha and the Mahanadi, along with the Chilka Lake area form one united focus ;
5. The endemic areas of the Godavari, the Kistna and the Cauvery are mostly restricted to the deltaic regions below the respective anicuts or in the areas irrigated by a system of canals issuing from the anicuts ;
6. The Bengal focus sends out two horn-like extensions into the Sylhet District of East Bengal and along the Brahmaputra river ;
7. The West coast is free from endemic areas and even the deltas of the Indus, Narbada and Tapti do not show any records of endemicity.

The Hilsa fish of India is essentially a brackish water species, corresponding in its migratory movements to the American Shad or the European Herring. In the Ganges and the Brahmaputra, where there are no protective engineering works and the annual floods are heavy and regular, the Hilsa ascends in the Ganges as high up as Kanpur and Agra and in the Brahmaputra as far as Goalpara. During flood the extensive Bheel areas of Sylhet become connected with the river system and receive copious supplies of Hilsa. The movement of Hilsa in the Mahanadi, Godavari, Kistna and Cauvery is restricted by the anicuts and its main fishery lies below them. Both the Narbada and the Tapti are fast rivers from a distance of 50 to 70 miles from their mouths and therefore, Hilsa fishing on a comparatively small scale is prevalent in their lower reaches only. It is well known that Hilsa congregate below obstructions and the strong currents of the Himalayan rivers joining the Ganges in all probability obstruct their upward ascent and thereby give rise to a fishery, corresponding to the inland focus of infection in Bihar and U.P. It will thus be seen that Swaroop's map drawn to show the main areas of endemicity of cholera in India could also be called the map of the Hilsa fishery. It must, however, be remembered that whereas considerable research has already been done on the endemicity of cholera, our knowledge of the Hilsa fishery has not yet received any statistical treatment. It would suffice for the present to note that Hilsa fisheries are mainly localised in those areas which are also the areas of high endemicity of cholera. The question of the Indus delta will be discussed separately.

SEASONAL VARIATION OF CHOLERA AND HILSA FISHERIES CORRELATED

In the non-endemic areas generally, cholera outbreaks occur during or following the rainy season. In some of the endemic areas, on the other hand, the months of high rainfall record low incidence of the disease. In the endemic areas of Bengal, for instance, the incidence of cholera begins to increase in the month of November and continues to rise till January. A minor decrease occurs in the month of February. Thereafter, the incidence increases in March and April and is at its minimum during the rainy months of July and August. Some of these observations can be correlated with the bionomics of Hilsa. It is now an established fact that Hilsa lives throughout the year in the estuaries and foreshores of the rivers in which it migrates during the flood season. The endemicity in the estuarine areas or the lower reaches of the river can therefore be associated with the presence of Hilsa in these waters throughout the year. Owing to tidal effects, there is always a considerable depth of water in these estuarine areas.

In the case of other endemic areas, where the cholera outbreaks are associated with rainfall, *e.g.*, Cauvery delta, it must be noted that the movement of Hilsa upriver can only be facilitated by floods caused by rains, because during the dry periods, river like the Cauvery, dries up below the anicuts, or the water level falls so low, that Hilsa, which usually moves in a depth of 6 to 12 feet of water, cannot undertake its migratory movement; thus the upriver movement of Hilsa beyond tidal limits can be associated with the flood season. It is necessary at this stage to recall the main phases in the wanderings of Hilsa in Bengal waters.

These are :—

(1) During the flood season, the adult Hilsa mostly swarm up the rivers for breeding purposes and move midwater. They probably breed in the lower reaches of the rivers. Some immature fish associated with these swarms move up but they probably breed much higher up next year ;

(2) The young fall back to the sea or estuarine areas and move near the bottom in the Hooghly at Nawabgunge ; their number is highest in October-November and the size smallest ; and then the number decreases and the size increases upto February ;

(3) About the same time, from November to February, the young (the progeny of the earlier breeders), which had migrated to the sea during the flood season and have already grown to 7 to 9 inches, approximately at the rate of 1 inch per month, form a big fishery during this season ;

(4) In March and April, the young, known as *Jatka*, enter East Bengal waters in large swarms and form an important fishery. In fact, the forecasting of the Hilsa fishery (top during the flood season) depends upon the numbers of the *Jatka* fish that come up during this season. It is not a breeding phase but a feeding phase ;

(5) These swarms probably move upriver and fatten as they go up and up, and mature in the middle and higher reaches of the river. The upward movement of *Jatka* is probably facilitated by the increase in volume of water in the rivers due to the melting of the snow in the Himalayas during the spring and hot months.

In Bengal, though the peak period of Hilsa fishery lies in the months of July, August and September, the incidence of cholera is generally the lowest during these months. The second, though minor, peak of Hilsa fishery is during the Nor' Western season and there is also a decrease of cholera cases during those months. This raises the question whether adult Hilsa of a foot or more in length, which generally migrate during the flood season, have anything to do with the endemicity of cholera? With the rise of water during the flood season, the Hilsa move midstream, whereas with the fall of water the Hilsa go to the bottom and move up or down, as the case may be, near the bottom. It would thus seem significant that cholera outbreaks are associated with the periods when the Hilsa are moving near the bottom of the water where cholera vibrios are likely to flourish away from the light. This would suggest that Hilsa probably carry infection when they are forced by water levels in the rivers to reside near the bottom.

The likelihood of young Hilsa, moving upriver near the bottom, being the "reservoir of infection" is further strengthened by the fact that as we travel westwards from East Bengal, where *Jatka* appear in February-March, the season of high cholera incidence is gradually delayed. In the districts of Howrah and Hooghly, April is the peak month for cholera. In Bihar, the peak occurs in the month of May and in United Provinces, in the months of June, July and August. This shift in the seasonal variation of cholera need not necessarily be due to infection being conveyed by human population, because, inspite of the rapid means of communication now available as compared to half a century ago, cholera has not shown a tendency to occur earlier in Bihar and United Provinces. The disease travels upstream from Bengal along the Ganges up to Allahabad and further north-west. This can also be explained on the movements of the shoals of young Hilsa in the river. The movement of these fish is from the sea upstream and thus some degree of correlation can be stated to exist between their movements and the upstream travelling of the disease from Bengal. For details of the wanderings of Hilsa, one of us (Hora, [1] 1941) has already given a fairly comprehensive account. From the perusal of that account and from what is stated above, it will be seen that some correlation does exist between the movements of Hilsa during the various seasons and the seasonal variations in cholera.

PHYSICAL FACTORS AFFECTING HILSA AND CHOLERA VIBRIO CORRELATED

During floods, owing to large quantities of detritus being washed into the river, the physical properties and the chemical composition of the water change considerably. In this connection attention may be drawn to some oceanographic studies in Indian waters by Sewell [4] He has stated :—"In an area such as the Bay, that is exposed at different times of the year to such opposite influences as the South-West and North-East monsoons, and into which most of the large rivers pour their water, one would naturally expect to find that the conditions present in surface waters would show a considerable range of variation both as regards the salinity of water and its temperature."

It would appear that the salinity of the Arabian Sea water is much higher than that of the Bay of Bengal. Sewell[4] has noted the changes in the salinity of water in the Bay of Bengal through different seasons of the year. The following figures will give the range of variation :—

TABLE. *Showing the Range of Variation,*

Months	Bay of Bengal	Laccadive Sea
September-November	20	36
December-February	30	36
March-May	32	35
June-August	30	35·5

It has to be noted that in each season still lower figures of salinity have been obtained in the area close to the mouths of the Ganges and the salinity was found to increase gradually towards the south. It will also be noted that the figures for salinity have not shown much variation in the Laccadive Sea, *i.e.*, part of the Arabian Sea. If the high salinity is detrimental to the survival of the cholera vibrio, the freedom of the West Coast and the Indus delta from cholera can be readily explained. It is indeed suggestive that the most suitable medium for the survival of the cholera vibrio is the so called 'diluted sea salt mixture'.

It would be interesting to investigate what effect these seasonal variations in salinity in the Bay of Bengal will have both on the physiology of the fish, as well as on the cholera vibrio. The changes in the salinity near the mouth of the Ganges river will also affect, to some extent, the composition of the estuarine waters further inland. For example, it is known that in the mouths of large rivers, there is always a stratification of waters according to density which is governed by relative salinities (Hora[1] 1943). There is thus a wedge of sea water in the mouth of the Ganges, its extent varying from season to season according to the availability of fresh waters to keep it in check. During the dry season this wedge penetrates far inland, thereby perhaps facilitating the movement of young Hilsa high up in the river during February-April.

Several workers have drawn attention to the possible relationship between the incidence of cholera and certain meteorological factors, *e.g.*, rainfall, humidity, temperature and pressure, *etc.* Russell[3] who has analysed the relevant data in this connection, has stated that, so far at least, two factors are concerned, namely, rainfall and humidity, and their close relationship can be accepted. It may be that the correlation which has been observed between these factors and cholera incidence is there, because of the influence of those factors on the bionomics of fish.

OTHER FACTORS OF CHOLERA ENDEMICITY CORRELATED WITH THE HILSA FISH BIONOMICS

Bacteriological studies have shown that (1) high organic content, (2) suitable concentration of salts and (3) absence of lethal effect of sun's rays, are the favourable conditions for the survival of vibrios. Al these requirements are fulfilled in the normal environment of Hilsa when it is migrating up or down near the bottom. As stated already, Hilsa ascend the rivers after freshets, when much detritus gets washed into the river and thereby raises the organic content of the water. The resulting muddiness of the water and the habit of the Hilsa to move at considerable depths ensures the safety of the cholera vibrio from the lethal effect of the sun's rays. So far investigators have used surface waters for determining the presence or absence of cholera vibrio in a body of water, but if our surmise is correct, bottom water samples may yield some positive results with regard to the occurrence of cholera vibrio in the Bengal rivers. In the tidal reaches of the rivers, where the waters are being constantly churned up, there can be no question of the deficiency of oxygen at the bottom for cholera vibrio to live.

Krishnan has carried out studies on the persistence of cholera vibrios in natural waters. As a result of the examination of 523 samples of natural waters during 1950 (236 from the river Hooghly, 113 of canal water at Calcutta, 114 of Calcutta Corporation bathing tanks and 60 from Tolly's Nullah at Calcutta). "The Hooghly river water proved to be a more constant source of vibrios than the canal water. No cholera vibrios were isolated from Corporation bathing tanks or from Tolly's Nullah." These results are directly correlated with the occurrence of Hilsa in natural waters near Calcutta. The Hooghly river, being an estuarine creek, harbours Hilsa throughout the year while the canals are occasionally fed from the Hooghly or the Kulti Rivers and thereby may get small populations of Hilsa. Hilsa has not yet been recorded from the Corporation bathing tanks, or from the Tolly's Nullah as there are no deep channels connecting them with the river Hooghly.

With regard to the Hilsa fishery, there are some popular beliefs among Bengal fishermen which indicate that Hilsa avoids light during its upward migration and moves near the bottom. It is stated that Hilsa can be kept alive in fishermen's boats on dark nights for 2 to 3 hours. Generally it is very susceptible to light and dies as soon as it is taken out of water. Hilsa becomes playful and comes to the surface on cloudy days when there is some drizzle and an east wind is blowing. On such days, they can be caught in large numbers. In Sangla Jal in the Sundarbans, Hilsa are mostly netted in the lower portion of the net.

PERIODICITY OF CHOLERA EPIDEMICS AND OF HILSA FISHERY

Russell[3] has demonstrated that there is a six-yearly periodicity in cholera epidemics in most of the Provinces in India. In his initial analysis, however, he had noted that this statement would not hold good in the case of Bengal and Assam where such a periodicity was not noticed. According to him, this was indeed, an argument to support the statement that Bengal was the home of cholera since the disease was endemic there at all times. Subsequently, Russell[3] examined the cholera statistics for the four main divisions of Bengal separately, in the same manner as was done for the different areas in the Madras Province. This statistical treatment brought out differences in cholera endemicity in the two areas of Bengal lying to the East and West of the river Ganges. In the area lying to the West, *i.e.*, Presidency and Burdwan divisions, six-yearly cholera periodicity was noted, while in the area lying to the East of the Ganges, *i.e.*, Rajshahi, Dacca and Chittagong divisions and Assam, a five-yearly periodicity was obtained. Russell stated as follows :—"On the other hand, the five-yearly periodicity, which has been shown to exist in the Eastern areas of Bengal and in Assam, differentiates those tracts from every other part of the Indian Peninsula, and makes one ask if these areas may not be most intimately concerned with the origin and spread of the cholera waves which travel westward and to the south. Further speculation on this question may, perhaps, be left for the future until additional facts as to the epidemiology of the disease have been elucidated."

Indeed, as Russell[3] himself has stated, "the problems associated with the epidemiology of cholera are not so simple as to be explained by a cyclic trend."

It is, indeed, interesting to note that one of us (Hora[1], 1941) has already suggested a five-yearly peak in the cycle of the fishery of Hilsa. A perusal of the map of Bengal and Assam will show that the main river Ganges flows through the Rajshahi-Dacca-Chittagong Divisions and that the branches of the Ganges passing through the Burdwan and Presidency Divisions carry very little fresh water to the sea. Hilsa fishery is mostly confined to the former divisions and not so intense in the latter. Before partition, most of the fish sold in Calcutta used to be the Padma Hilsa. The five-yearly Hilsa cycle determined by Hora[1] on the basis of specimens taken at Goalundo on the Padma river in East Bengal, is interesting. On the other hand, the Burdwan Division of Bengal, or at least the Northern part of it, is comparatively a dry area with little chances of Hilsa being found there in any abundance. In the light of this evidence, the correlation between five-yearly peaks in Hilsa fishery and in cholera epidemic in Eastern Bengal is, indeed, very interesting. It would appear that the question of any correlation between peak periods of Hilsa fishery and the periodicity of cholera will have to be investigated anew with special reference to the endemic areas of cholera in India.

THE ROLE OF HILSA IN SPREADING CHOLERA

Hilsa belongs to the category of "Fat" or "Black" fishes which signifies their high body-oil content and makes them liable to putrefaction within a short period after their removal from water unless suitably processed. During the season, particularly in the neighbourhood of fishing centres, it is very cheap and during years of abundance, such as occurred in 1934, 1939 and 1944, large quantities of Hilsa were left to decompose on the river banks or buried in trenches. It is, therefore, likely to be eaten in excess by the poor and owing to richness of its flesh is likely to cause mild gastro-intestinal disorders which may serve as a predisposing cause for an attack of cholera. Such a course of events might explain why inspite of *considerable infestation of the population* with cholera vibrios during a severe epidemic, certain individuals alone develop the disease while others escape the infection. The question of the presence or absence of such a predisposing factor will have to be taken into consideration in any discussion regarding the choleragenicity of the vibrio apart from any intrinsic differences in the strain of *Vibrio choler ae* which are yet to be determined.

In Bengal special care is taken not to eat the pseudobranchs, hypyural region and the nerves of the lateral line organs. In preparing Hilsa for the table, cooks throw these parts away. The significance of this practice is not clear to us and needs investigation.

Even if Hilsa were to harbour the infection, how does it actually transmit the disease to human beings? The explanation for this, perhaps, lies in the methods of handling the fish. The gills and the viscera are liable to undergo putrefaction very rapidly, so they are removed first; and generally thrown away. The fish is then washed which permits the infected intestine to transmit the infection to some water source. In other words, this procedure is not dissimilar to the dispersal of the vibrios in the environment through fæcal matter. In some places, the poor eat the intestines also. These habits can thus be important in the spread of cholera through fish. It is interesting to note that the Hindus of Bengal are enjoined not to eat Hilsa from the last day of Durga Puja (end of September or beginning of October, sometimes even middle of October) to the Sri Panchami day (end of January to the beginning of February). This period of 3½ months coincides with the peak period of cholera in Bengal, *i.e.*, November to January.

WORLD DISTRIBUTION OF CHOLERA

On page 30 of his review, Taylor[5] has pointed out that the area of major true endemic centres are Lower Bengal and the Yangtse Valley. The probable endemic areas in addition, are a portion of Central and Southern Madras, Burma and the Philippines. Here also there is a strange coincidence, for, in the Yangtse Kiang River, *Hilsa reevesi* forms as important a fishery as *Hilsa ilisha* in the Ganges System. *Hilsa ilisha* also ascends into the Irrawadi and Salween rivers of Burma where it forms important fisheries. We have already considered the Hilsa fishery of Peninsular India which is restricted to the deltaic portions of the rivers and to brackish water lakes. Thus extensive Hilsa fisheries exist in the two major true endemic areas and also along the east coast of Madras and in Burma. *Hilsa reevesi* of the Chinese water is also found in the Philippines, so the extension of cholera to that area can also be explained on the basis of Hilsa fishery in the Philippine waters.

Hilsa ilisha also ascends the Tigris and the Euphrates from the Persian Gulf and into the Indus from the Arabian Sea. Information regarding the endemicity of cholera along these rivers is lacking but as is suggested elsewhere cholera may be absent from those areas on account of the high salinity of the Arabian Sea (*vide supra*,) as compared with that of the Bay of Bengal or at the mouth of the Yangtse Kiang. Moreover, the Indus floods are due to the melting of snow and the waters are so clear that Hilsa can be speared. As the cholera vibrio shuns light, its absence in the Indus basin may be due to this factor.

The presumption that higher salinity of certain seas may be the factor that probably controls the distribution of cholera is further strengthened by the fact that species of Hilsa that are restricted to the seas and do not ascend into fresh waters, there is no cholera in the areas of their distribution. Such species are *Hilsa durbanensis* from Natal and the Portugese East Africa; *Hilsa toli* found from the seas of India through the Malay Peninsula to Formosa and China; and *Hilsa macrura* of the seas of the East Indies. The species that enter fresh waters and may carry infection are *H. kelee* of the Mekong River; *H. brevis* of the East Indies; *H. reevesi* of China and the Philippines and *H. ilisha* of the Persian Gulf, India and Burma.

PANDEMICS OF CHOLERA

This leads us to the consideration of another interesting hypothesis. Pandemics of cholera are known to have occurred in the eighteenth century, the infection having started from its 'home' in the Delta of the Ganges and reaching other countries via the sea and land routes to Europe and even U.S.A. It would be interesting to speculate whether such pandemics could not have been due to the migration of infected fish. Some of these pandemics, after having reached the shores of other countries, have spread upstream from the point of entry. This may, of course, seem a far-fetched hypothesis, but its probability is suggested in view of the following remarkable cases of marine fish dispersal. Professor Meggitt of the Rangoon University made a large collection of fish at Maunmagan, Mergui Archipelago, Burma and obtained five Atlantic species of European waters (Hora and Mukerji[2], 1936). It has recently been ascertained by Hora[1] in correspondence with an eminent Indonesian fishery biologist, that a Cichlid marine fish of Africa (*Tilapia mossambica*) was collected by an Indonesian from the Javanese waters, and that the progeny of those very individuals is now being extensively used for cultural operations in Indonesia. How they got dispersed over such wide areas is not the subject for discussion here. Probably sea currents or cyclones of abnormal intensity could bring about such a dispersal.

CONCLUSION

We are conscious that the statements made in this paper will appear somewhat dogmatic and even premature. The object of this note, however, is to focus attention on this new approach to the study of the problem of endemicity of cholera in India, and the probable role of Hilsa in maintaining it. In order to prove or disprove this hypothesis, a considerable amount of collation of existing data will be necessary and field work and laboratory work on several aspects of the problem will have to be initiated. Experimental infection of fish in any suitable *manner may yield interesting results. It is suggested that this may be* attempted in the first instance. If the results of the preliminary studies are suggestive, the work can be extended in several directions including bacteriological, biochemical and epidemiological, statistical and other aspects of the problem. It is felt that, at any rate, a *prima facie* case has been made for such studies.

REFERENCES.

1. Hora, S L : Life-History and Wanderings of Hilsa in Bengal Waters, J. Roy. As Soc. Bengal Sc, **6** : 93-112, 1941.

   ——Evidence of the Distribution of Fishes Regarding Rise in the Salinity of the River Hooghly, Curr. Sc. **3** : 89-90, 1943.

2. Hora, S. L. and Mukerji, D. D. : European Species of Fish from the Tavoy Coast, Burma, Nature, **136** : 152, 1936.

3. Russell, A. J. H. : Epidemiology of Cholera (I), Ind. J. of Med. Res., **13** : 427-433, 1925-26.

   ——The Epidemiology of Cholera (II), Ind. J. of Med. Res., **13** : 637-648, 1925-26.

   ——Epidemiology of Cholera (III), Ind. J. of Med. Res., **14** : 1-6, 1926-27.

4. Sewell, S. R. B. : Geographic & Oceanographic Research in Indian Waters Part V—Memoirs of the Asiatic Society of Bengal, **9** : 207-356, 1929.

5. Taylor, J. : Cholera Research in India 1934-40 Under the Indian Research Fund Association. A Review : Special Report I. R. F. A., No. 5, 1941.

TREATMENT OF PULMONARY TUBERCULOSIS WITH COLLAPSE THERAPY AND CHEMOTHERAPY †

J. N. Berry *

The 250 beded medical wing of the Medical College Hospital, Nagpur was started at Ajni (Nagpur) on the 8th of October, 1950. The hospital is divided into two units, each of which has twenty beds reserved for cases of pulmonary tuberculosis. This paper records the results of the use of these beds in Unit No. II under the care of the writer upto the end of January 1951. Some of the cases also had been under the care of the writer in the Mayo Hospital, Nagpur, where the medical wing had been functioning earlier.

Only cases of bronchogenic or adult or reinfection type of lung tuberculosis have been included. Primary and hæmatogenous types are not included.

The paper is designed to show the short term results of collapse therapy combined with specific treatment, and raises important points with regard to making greater use of these 20 beds by combining domiciliary treatment along with a short period of hospitalisation.

MATERIAL

There are eleven beds for males and nine for females. Thirty-nine patients, 22 males and 17 females were treated on these 20 beds in the period (16 months) under review. Their age incidence is given in Table 1.

TABLE 1. *Age Incidence.*

Age in years.	Male total. 22	Female total. 17
14 Years ..	1	..
15—20 ..	4	6
21—25 ..	11	3
26—30 ..	3	2
31—35 ..	..	3
36—40 ..	..	..
41—45 ..	1	1
46—50 ..	1	1
51—55 ..	1	1

As seen in Table 1, 60 percent of the cases amongst both sexes were in the age group 15 to 25. Though the figures are small the females reach their highest incidence at a younger age (15-20) than the males (21-25). There was one case each in the age group of 51 to 55.

---

† A paper read in a Symposium on Treatment of Pulmonary Tuberculosis held on the 19th and 20th February, 1951 in Medical College, Nagpur.

* From the Department of Medicine, Medical College Hospital, Nagpur.

The presenting symptoms and their duration were as follows:—

Presenting Symptoms :—

1.	Cough with or without expectoration and fever ..	All except two cases.
2.	Pain in chest with cough and fever (including one with precordial pain radiating down the left arm) ..	16 cases.
3.	Hæmoptysis	1 case.
4.	Vomiting, flatulence and eructation	1 case.
5.	History of hæmoptysis (including those getting it during stay in hospital	9 cases. 23%.

Duration of symptoms on reporting :—

Less than ½ month	5 cases.
½ to 1 month	5 cases.
1 to 2 months	8 cases.
2 to 3 months	6 cases.
3 to 6 months	7 cases.
6 months to 1 year	5 cases.
1 to 2 years	2 cases.
More than 2 years	1 case.

It is interesting to note that cough and fever were complained of by all but two cases and that 31 out of 39 cases, *i.e.* 80 percent reported within six months of noticing the symptoms.

EXTENT AND TYPE OF DISEASE

Out of 39 cases, 25 cases showed bilateral disease radiologically, *i.e.*, 64 percent were bilateral on admission. Out of the 14 unilateral cases, 3 became bilateral while in hospital. The total extent of the disease, including flare-ups and spreads, was assessed radiologically. Disease extending upto one zone was present in 6 cases, upto two zones in 9 cases, three in 14 cases, four in 3 cases, five in 2 cases and disease involving all the six zones in 5 cases. It shows that 24 cases, *i.e.*, 62 percent had involvement of equivalent of one lung or more at some stage of the disease in the hospital.

For clinical assessment of the cases and the results of treatment, the classification approved by the Ministry of Health, Great Britain and contained in Ministry of Health Memorandum 37/T (revised) as quoted by Heaf and Rusby [8] (1948) has been used.

TABLE 2. *Classification.*

		Male. 22	Female. 17	Total. 39
Sputum Negative	A1 ..	2	1	3
	A2 ..	4	1	5
	A3 ..	..	..	..
Sputum Positive	B1 ..	..	..	..
	B2 ..	9	10	19
	B3 ..	7	5	12

Table 2 shows the classification of the cases. It is interesting to note that nearly 1-3 of the cases come in B3 group.

COMPLICATIONS

Hæmoptysis occurred in 6 cases, tubercular entero-colitis in 5 cases, tubercular laryngitis in 3 cases, tubercular tracheo-bronchitis in 7 cases, fistula in ano in one case, spontaneous pneumothorax in one case, secondarily infected tubercular pyo-pneumothorax (tension pneumothorax) in one case, tuberculosis of the kidney in one case, tubercular arthritis in one case, lupus, vulgaris in one case, S.O.M. tubercle in two cases, phylctenular keratitis in one case, diabetes mellitus in one case, sub-acute cor pulmonale in one case, asthma in one case, non-co-operation, obstinacy, refusal to take food in one case, flatulence nausea, vomiting in two cases and herpes zoster in one case. Tubercular tracheo-bronchitis was diagnosed clinically on the basis of excessive dyspnœa, or paroxysmal cough unexplainable by the roentgenological picture or because of large tension cavities or segmental or lobar collapse-consolidation radiologically. Bronchoscopy was not done in any case.

TREATMENT

General:—All patients were put on ordinary hospital diet consisting of 3,600 calories, containing protein 128 Gm., carbohydrate 750 Gm. and fats 96 Gm. till a few months ago after which the hospital diet consisted of 2,800 calories, carbohydrates, 532 Gm., fats 72 Gm. and proteins 83 Gm.

Along with this each patient was provided with one pound of milk extra and one egg, the later having been replaced by one oz. of Horlicks recently.

In all cases bed rest was enforced on admission and kept up till a fortnight after the temperature reached normal. Later, they were allowed to move about gradually. No rigid control of bed rest or graduated exercises were given or possible.

All patients had their weekly weight and E.S.R. (corrected for anæmia) taken. Chest roentgenograms and sputum examinations were done monthly. Culture facilities have been made available recently. Arrangements for streptomycin and P.A.S. resistance tests are being made.

Flouroscopy was done regularly in every case by the writer before each refill whether A.P. or P.P. 250 to 300 cc. were given on the induction of A.P. and 350 to 500 cc. at re-fills. Pressure was always kept negative. 500 to 600 cc. were given at the induction of artificial P.P. and 800 to 1,000 cc. at the re-fills. Pressure was left at plus 3, plus 4 and not allowed to exceed plus 6.

No re-fills, except in the case of one patient who needed it every 3rd or 4th week, were given at more than fortnightly intervals whether A.P. or P.P.

Collapse therapy and specific treatment were given as shown in Table 3.

TABLE 3. *Type of Treatment.*

	Male.	Female.	Total.
A. P. (unilateral)	6	5	11
Phr. crush with P. P. ..	5	10	15
Phr. crush alone	1	..	1
P. P. alone	1	..	1
Phr. crush with P. P. & with A.P. opp. side	1	1	2
Internal pneumolysis			
Done ..	4	1	
Due ..	..	3	8
Thoracoplasty	2	..	2
Monaldi's suction	1	..	1
Drainage	..	..	..

Artificial Pneumothorax :—The aim of collapse therapy is to relax the lung and closure of the bronchus communicating with the cavity resulting in its obliteration. Cavity closure usually leads to sputum conversion. Local rest of the lung, lymph stasis and hyperæmia in the collapsed lung are some of the other important effects. It is indicated in all cases with a fibrocaseous type of disease with cavities. All cases of pulmonary tuberculosis are assumed suitable unless proved otherwise. In unilateral disease, if of the acute exudative type with severe toxæmia and a sedimentation rate more than 40 mm., it is better to wait till the case settles with bed rest or in some cases with the help of streptomycin. Dorsal lobe cavities and basal cavities do not fare as well with A.P. The large peripheral apical cavity is seldom suitable because of the dense adhesions, often total. A very fibrous type of disease, often with emphysema and low vital capacity, and tubercular tracheo-bronchitis are two other relative contra-indications, as also bilateral disease when extensive. Often, keeping the aim of cavity closure and sputum conversion in mind, a trial pneumothorax as advocated by Young[36] (1949) may have to be done. That sputum conversion is most important for successful long range results is shown by the study of Livingstone[17] (1949).

Data with regard to the type of disease, complications, duration of A.P. and results in the 11 cases that were treated with A.P. is given in Table 4.

It is interesting to note that pleural effusion was present in 1 case only and that too was minimal. Other complications were obliterating

TABLE 4. *Results of A. P. Treatment.*

No.	Name.	Type and extent of disease.	Duration of A.P. in months.	Complications.	Internal. Pneumolysis.	Other treatment.	Result.
F. — 4.	M.B.	Unilateral.	8	Adhesions band shaped sub-apical.	Done two stages. Not effective. Severe sub-cut. emphysema involving face.	—	Quiescent.
F. — 6.	S. B.	Bilateral active disease.	2	Obliterating pleurisy.	—	Strep. Phr. cr. P. P. Contra-lateral.	Active.
F. — 7.	Mrs. R.	Unilateral.	1¼	Sub-apical adhesions. Spont. pneumothorax.	Due for internal pneumolysis.	—	Quiescent.
F. — 16.	V. B.	Bilat. Now chiefly Rt. mid. zone cavity.	1	Adhesions sub-apical.	Due for interal pneumolysis.	Previous Phr. cr. & P.P. same side	Active.
F. — 17.	M.	Unilateral.	1	Thick pleura, complains of pain after refills larger than 300 cc.	Due for internal pneumolysis.	—	Active.
M. — 9.	G.N.S.	Bilateral,	1	—	—	Phr. cr. P.P. other side. Strep. & P. A. S.; 8 M.	Recently Active.
M. — 16.	B. B.	Unilateral.	12	Pleural adhesions. Severe pain after A.P. once only 100 cc. Needs refills every 3 to 4 weeks.	In two stages. Marked sub-cut. emphysema.	—	Selective collapse Quiescent.

TABLE 4. *Results of A. P. Treatment.—(contd.)*

No.	Name.	Type and extent of disease.	Duration of A.P. in months.	Complications.	Internal. Pneumolysis.	Other treatment.	Result.
M.—2.	K. K.	Bilateral	2	Apical pleural adhesions.	In two stages, not effective.	Strep. P.A.S.	Active.
M.—7.	D. R.	Bilateral.	4	Sub-apical and basal adhesions.	Done. Marked sub-cut. emphysema. Due for internal pneumolysis again to cut a basal adhesions.	Strep to control flare upon on other side.	Active Selective collapse.
M.—17.	N.	Rt. dorsal lobe cavity with infilt. around.	10	Adhesions. Pleural fluid just obliterating the angle.	Done.	Strept. P.A.S. for tub. kidney.	Selective collapse Active recently.
M.—19.	B.	Bilat. Up. zone infilt.	17	Basal adhesions. Mobile mediast. Mediast. hernia. Sub-cut. emphysema. Breaking of Morland's needle point in pleural sinus.	—	Strept. for flare up on the other side	Quiescent Ambulatory.

TABLE 5. *Phrenic Crush with P. P.* (15 *cases.*)

No.	Name.	Type and extent of disease.	Indication for P. P.	Duration of P. P.	Complication of P. P.	Complications of Phr. crush.	Treatment.	Result.
F. — 11.	T. B.	Bilat. exudat. Dis. Lt. Up. and Mid. *zone*. less extensive on Rt. side.	Toxæmia Fever and E S.R. Bilat. exudat. Dis.	5 months. Phr. crush twice.	—	Twice failed Gr. 3.	Later A. P. Lt. unsucc.	Active.
F. — 12.	D. D.R.	Bilat. extensive exudat. dis.	Toxæmia High fever A. P. Rt. abandoned previously. Phr. crush done before admission.	5 months.	—	—	Strepto. P.A.S.	Active. Left hospital in extremis.
F. — 13.	T. B.	Bilat. Acute exudat. dis.	Rt. basal pleurisy & consolid.	5 months Phr. cr. twice. 2nd 3½ months later.	Periton. adhesion Rt. Up. quad. in 1st refill.	—	Strepto.	Quiescent.
F. — 14.	K. B.	Exudat. Dis. Both Up. Zones. Rt. more than Lt.	Asthma. A.P. Rt. Contra select.	12 months.	Periton. adhesions Both Up. quad. late.	2nd Phr. failed. Gr. 2.	Anti spasmodics.	Active recently.
F. — 16.	V. B.	Rt. Up. Lobe collapse consolidation. Acute exudat. Dis.	Acute exudat. Dis. with toxæmia. —	16 months. Phr. cr. twice.	Periton. adhesions Rt. Up. Quad., late. (2) Acute dermatitis due to Tr. benz. co. (3) Sub-cut. emphysema during P.P., once accidental leak from apparatus.	2nd Phr. failed Gr. 1. (2) Pleural bone opened accidently.	A. P. Successful same side Strepto.	Active.
M. — 9.	G.N.S.	Bilat. Acute Exudat. Dis. Rt. U. & M. zone. Lt. Mid. *zone* infilt.	Bilat. Dis. Acute exudat. with toxæmia.	8½ Months. Phr. cr. twice.	Peritoneal adhesion Lt. Up. quad. early.	—	P.A.S. Strepto. A. P. Rt. Contra select. A.P. Lt.	Active.
M. — 4.	G. D.	Pleurisy and Lt. Mid. zone infilt.	A.P. Lt. Contra select.	6 months Phr. cr. twice.	Scrotal Pneumocele, once.	—	—	Quiescent.

TABLE 5 *Phrenic Crush with P. P.* (15 *cases.*)—(*contd,*)

No.	Name.	Type and extent of disease.	Indication for P. P.	Duration of P. P.	Complication of P. P.	Complications of Phr. crush.	Treatment.	Result.
M. — 18	S. R.	Bilat. Up. zone infilt. with cavitation in Lt. Up. zone.	Thick pleura Lt. Up. Zone.	13 months Phr. cr. twice.	Tension Cavity Lt. Up. Zone.	—	Strepto. P.A.S. Monaldi Suct. Dr.	Quiescent.
M. — 20	R.	Acute exudat. Dis. Lt Up. & M. zone with large cavities.	Toxæmia Acute Exudat. Dis.	12 months.	—	—	Strepto.	Died.
M. — 21	V. N.	Bilat. Acute exudat. Dis. Rt. Up. & Mid. & Lt. Mid. Zone.	A.P. Rt. failed.	5 months.	—	—	Earlier Strepto. & P.A.S.	Active.
F. — 1	C. B.	Assman's focus.	Toxæmia. High Temp.	8 months.	—	—	—	Quiescent. Ambulatory.
F. — 2	A P.B.	Acute Bilat. Dis.	Rt. basal consolid & cavit.	1 month.	—	—	Strepto. I.V.Ca.	Left hospital in extremis.
F. — 5	I. B.	Unilat. Acute Exudat Dis.	High Temp. E.S.R. 52.	7 months. Phr. cr. twice.	—	Lt. vagal Cr. in place of Lt. phr. nerve.	Strepto. A.P. Contra Select.	Active.
F. — 6	S. B.	Bilat. extensive Exudat. Dis.	Evidence of Toxæmia. High fever E.S R.	7 months.	Pneumo-Midiast. After P.P. 4-6	—	Strepto. A.P. Rt.	Active.
F. — 9	P. S.	Collapse consolid with cavitation Rt. Up. zone & Infilt. Lt. M.Z.	A. P. Rt. failed.	1 month.	—	Failure.	Strepto. P.A.S.	Active.
M. — 1	P. K.	*P. P. Alone. One Case.* Bilat. Extensive Mottling.	Bilat Acute Exudat. Bronch. pneumonia.	5 months.	—	—	—	Active.
M. — 5	R.	*Phr. Crush. Alone* Fibrocaseous dis. Rt. Up. zone.	*One Case.* A.P. Rt. Contra Select.	—	Refused P.P.	Diaphragm raised by small intest loops.	—	Died.

pleurisy in one case and spontaneous pneumothorax in another. One case showed at the first refill a mobile mediastinum, mediastinal hernia and sub-cutaneous emphysema. In the same person the needle point of Morland's refill needle broke in the pleural sinus during a refill without any untoward effects. Pleural adhesions were present in nine cases. Some cases complained of pain occasionally during a refill. Eight out of these 11 cases were put up for thoracoscopy and possible internal pneumolysis. Out of the five, in whom internal pneumolysis had been attempted it was successful in three only. Marked sub-cutaneous emphysema after the operation was the only complication and was present in 3 out of five cases (pleural effusion has been noted in 2 out of these 5 cases as a late result since the reading of this paper).

Phrenic Crush with Pneumoperitoneum :—It is indicated in those cases where A.P. is not possible or advisable. Cases with basal cavities or dorsal lobe cavities or large peripheral apical cavities with dense adhesions, if thoracoplasty is not possible or advisable, will come under this category. Cases of acute exudative disease with toxæmia may be given the same till they "cool off" and are fit for A.P.

Pneumoperitoneum alone is indicated in bilateral basal or extensive disease.

Phrenic crush alone may be used to slow down the expansion of the lung when abandoning A.P. or sometimes may be combined with a partially effective A.P.

Fifteen cases had phrenic crush with pneumoperitoneum and their data including indication, duration, complications and results are given in Table 5.

In this series the indications for pneumoperitoneum with phrenic crush were acute exudative disease with toxæmia, fever and an E.S.R. above 40 mm. in seven cases, basal lobe disease in two cases, both females, and in seven cases either the A.P. induction was unsuccessful or contra-selective due to adhesions. One case with bilateral extensive disease got artificial pneumoperitoneum alone.

Complications of Artificial Pneumoperitoneum :—Scrotal pneumocele occurred in one case only. It was a medical college student who complained of pain and swelling in the left side of the scrotum a few hours after the pneumoperitoneum. On examination there was no abdominal or scrotal sub-cutaneous emphysema but there was crepitus on pressure over the left spermatic cord. It was surmised that the patient had a patent funicular process on the left side. Further refills were uneventful. It is a rare complication of artificial pneumoperitoneum but has been recorded previously amongst others by Rogers and Garrett [29] (1947) and Nagley [24] (1948). One female aged 20 got pneumomediastinum on the evening of the pneumoperitoneum. She complained of pain in the throat and difficulty in swallowing. On examination there was sub-cutaneous emphysema in the supra-sternal notch round the trachea but no subcutaneous emphysema anywhere else. It cleared off by the next day. In one case sub-cutaneous emphysema occurred due to an accidental leak in the apparatus and in another, acute dermatitis due to tinct. benz. co. used for sealing. 2 cases showed peritoneal adhesions early in the course of refills and two after 3 to 6 months of pneumoperitoneum. It is suggested that the early adhesions were the result of pre-existing tubercular peritonitis and the late ones due to adhesive peritonitis as a result of pneumoperitoneum. Peritoneal effusion was not detected in any case.

The complications of phrenic crush were not many except that in one case during a repeat operation 6 months after the first, the respirations stopped immediately after the crush, and later became jerky and irregular, and the pulse, feeble and rapid. Oxygen inhalation and intravenous coramine were administered. An hour afterwards the pulse rate fell to 120 per minute and became regular and the respiratory distress disappeared. A few days later the diaphragm was shown to be not paralysed on screening. It was surmised that there had been an accidental left vagal crush. In one case there was an accidental opening of the dome of the pleura and in another there was wound sepsis. The important feature was the failure of complete diaphragmatic paralysis to occur as judged by the absence of paradoxical movement on sniffing in front of the flouroscopic screen in the erect posture. Out of 21 operations, 6 were failures; 2 after primary operations (14) and 4 out of 7 repeat operations, one having failed both times. Mitchell[23] (1949) quotes 9 percent and 14 percent as failures in his series in first and second operations respectively. On further analysis of these five cases the hemi-diaphragm was found to be raised but showed less movement downwards in one each of primary and repeat operations; in two repeat operation cases the diaphragm was raised but movement was downwards and equal while in one case the diaphragm was not raised and movement was downwards and equal.

After a phrenic crush the diaphragm regained movement in three to six months but it remained raised for sometime afterwards.

Streptomycin Therapy:—In specific treatment only streptomycin and Para-amino-salicylic-acid (P.A.S.) were used. No cases got sulphetrone or *thiasemicarbazone (TB1/698) as neither was available locally.*

Streptomycin—Earlier, the report from the American Veteran Administration (Council on Pharmacy and Chemistry)[5] (1947), and Streptomycin Committee, Veterans Administration[30] (1948) had shown that streptomycin was likely to be of benefit chiefly in the exudative type of cases in the young adult which was unsuitable for collapse therapy. Indications for streptomycin in pulmonary tuberculosis were elaborated further in an Editorial in the Lancet[12] (1948) on the lines of Medical Research

Council[22] report (1948). It advocated the use of streptomycin for lesions unlikely to benefit from ordinary treatment (bed rest and collapse measures alone). It would include rapidly advancing disease (acute progressive bilateral tuberculosis of recent development in young adults) where pneumothorax was contradicted and acute 'spreads' (after A.P. or thoracoplasty) and lesions too hot for immediate A.P. This definition excluded fibroid or fibro-caseous lesions or long-standing cavitation, terminal conditions and also minimal early lesions with favourable prognosis. Other indications were tubercular laryngitis, tubercular tracheo-bronchitis, tubercular entero-colitis, tubercular sinuses and tubercular empyema.

The main drawback is the development of the resistant strain of tubercle bacilli in 6-10 weeks. Hence the maximum effect is within the first month or two and it is likely that one course only would be of value (Marshal[21] 1949). There is some evidence that resistance develops more rapidly in patients with large cavities. An official memorandum by the Streptomycin Sub-Committee of Standing Advisory Committee on Tuberculosis to the Ministry of Health, Great Britain (1949[32]) emphasised the same points and advocated its use in combination with other therapeutic measures and suggested that its major role may be to make possible the use of collapse procedures which in its absence would have had to be delayed or never performed.

A later preliminary communication from the Medical Research Council (1949) said that combination of P.A.S. 20 Gm., daily with 1 Gm. of streptomycin, considerably reduced the risk of development of streptomycin resistant strain of tubercle bacilli during the six months following the start of trial (period upto the time of communication).

The chief toxic symptoms were those pertaining to the eighth cranial nerve—vestibular disturbance, giddiness and inco-ordination in the dark, and nerve deafness. Others were renal damage in some cases and skin rashes including exfoliative dermatitis, drug fever and leucopenia probably of allergic origin. The toxic symptoms increased rapidly on using doses above 1 Gm. daily. In earlier reports, 2 Gm. daily were given but later reports (Streptomycin Committee, Veterans Administration[30] 1948, Medical Research Council 1949) advocated only 1 Gm. daily in two divided doses. Dihydrostreptomycin was said to be less toxic than streptomycin (Lancet[13] 1949a) and the use of iodide tended to diminish the required dose experimentally (Lancet[14] 1949b).

O'Conner [27](1949) stressed the importance of integration of streptomycin with other forms of therapy particularly collapse therapy. The Streptomycin Committee of the Veterans Administration [31] (1950) came to the conclusion that streptomycin alone can never be counted on to cure tuberculosis. On dosage, a recent report by Bignall *et al*[2] (1950) to the Medical Research Council concluded that 1 Gm. daily in a single injection without intermission of treatment is the most satisfactory way of giving the drug in pulmonary tuberculosis.

Para Amino Salicylic Acid (Sodium Salt):—P.A.S. has a bacteriostatic action and has been used in pulmonary tuberculosis and found of benefit in patients with acute exudative disease resulting in rapid diminution of toxæmia and improvement of the general condition (Erdie[6] 1948, Nagley & Logg[25] 1949, Vallentin *et al*[35] 1950). The chief toxic symptoms are gastro-intestinal disturbances—loss of appetite, nausea, vomiting and diarrhœa in some of the cases. Prolongation of the clotting time (Madigan *et al*[20] 1950) and rarely cardiac irregularities and paralysis due to potassium deficiency (Cayley[4] 1950) probably due to prolonged administration of the sodium salt, (Nagley[26] 1950) may occur. Its comparative freedom from toxicity and apparent *inability to produce resistant strains were its great advantages as compared* with streptomycin even though the effect was not so dramatic. But it has been shown that tubercle bacilli do develop resistance to P.A.S. in 4 to 6 months (Madigan *et al*[20] 1950, Carstensen and Andersen[3] 1950; Horne[11] 1950). Its importance has been much increased since the Medical Research Council Report (1949) that in 20 Gm. daily doses with 1 Gm. of streptomycin a day, it reduces the risk of streptomycin resistant strain.

It is chiefly excreted in urine where its contents will be specially beneficial in tuberculosis of the urinary tract.

In the present series, both streptomycin and dihydrostreptomycin were used as available locally. Potassium iodide was used simultaneously only in a few cases.

Out of 39 cases, 19 cases, *i.e.*, nearly half were given streptomycin, with or without P.A.S. at some stage of the disease during their stay in hospital. The large number of cases being given streptomycin inspite of the very restricted supplies is only a reflection on the number of cases with acute progressive bilateral disease.

The indications for streptomycin in these 19 cases were acute exudative spreading bilateral disease in seven cases, 'flare-up' and or spread in seven, tubercular tracheo-bronchitis in two, renal tuberculosis in one and tubercular entero-colitis in two cases.

Streptomycin was combined with collapse therapy in 4 cases. 3 received A.P., 9, phrenic crush with P.P. and 2, phrenic crush and P.P. with contra-lateral A.P.

In one case (No. 3F.) high fever occurred after three months of streptomycin administration due to the development of streptomycin resistance. In another it was possible to control a contral-lateral flare-up during the course of A.P. (Case No. 1 M.). Another (No. 2M.) illustrated the effect of streptomycin and P.A.S. combined with A.P. in a case with bilateral spreading acute exudative tuberculosis in a boy aged

19. A fourth (No. 9 M.) was a young man aged 22 who came with bilateral acute exudative pulmonary tuberculosis involving most of the right side and the left middle zone complicated by tubercular enteritis and much constitutional disturbance. He had streptomycin and P.A.S. for the longest period, *i.e.*, 9 months of the series. A fifth (No. 16 F.) was a young girl aged 25 who came with collapse-consolidation of the right upper lobe and inspite of phrenic crush and P.P. she got a spread on the same side and the other side was controlled by streptomycin. She is also the only case who showed any complication worth the name in this series. On the seventh day after streptomycin she developed an erythematous rash all over the body which went on to scaling and subsided after the use of benadryl 50 mg. three times a day. There was no neutropenia along with this exfoliative dermatitis. Exfoliative dermatitis due to streptomycin is a rare complication, (Harris & Walley 1950[7]).

P. A. S. :—It was used mostly in conjunction with streptomycin for its effect on the development of streptomycin resistance strain. The Medical Research Council Report (1949) recommended 20 Gm. a day but we aimed at 18 Gm. daily. Few patients could tolerate the full dose throughout the period of administration inspite of alkalies and giving the P.A.S. dose immediately after meals. The dose had to be reduced, often temporarily, to 10 to 12 Gm. a day. In no case was the gastro-intestinal upset enough to make us abandon the drug. Nine cases including one complicated by renal tuberculosis received P. A. S. with streptomycin. Only two cases were given P.A.S. alone. Case No. 15 F was one of these. Table 6 illustrates the results.

TABLE 6. *Overall Review of Results.*

Died.	Discharged own self in extremis. Presumably dead.	Discharged at own request.	Discharged for ambulatory treatment 'Quiescent'	Still in Hospital.	
				"Active."	"Quiescent"
Male 5	1	3	3	7	4
Female 1	3	1	1	8	3

Of 39 cases, 10 are "quiescent", 10 are dead or presumably dead and 19 are "active". Table 7 analyses the 10 dead or presumably dead cases further.

TABLE 7. *Analysis of "Dead."*

No.	Name.	Category and extent of disease.	Period of stay in Hospital.	Other remarks.
M. — 3.	J. B.	Bilat. B3.	15 days.	....
M. — 12.	R. C.	Unilat. A2.	1 month.	Died the day after thoracoplasty.
F. — 8.	K. B.	Bilat. B3.	3 days.	Came with Bilat. extensive Dis. with sub-acute Cor Pulmonale.
M. — 7.	M. K.	Bilat. B3.	1 month.	Secondary infected (B. Pyocyaneous) Tub. Pyo-pneumothorax.
M. — 11.	S. I.	Bilat. B3.	3 months.	Tub. entero-colitis.
M. — 5.	R.	Unilat. A2.	5 months.	Obstinate uncooperative refused to eat due to flatulance.
F. — 2.	A. P. B.	Bilat. B3.	3 months.	Tub. entero-colitis.
F. — 3.	A. L. B.	Unilat. B3.	6 months.	Diabetes mellitus.
F. — 12.	D. B.	Bilat. B3.	5¼ months.	Streptomycin resistance on admission.
M. — 19.	R.	Bilat.	14 months.	Large cavities.

It is interesting to note that out of the 10 dead or presumably dead cases, seven were bilateral and all the seven belong to B3 class on admission. Of the three unilateral cases, one had diabetes mellitus, another was uncooperative and refused to eat and the third died soon after the thoracoplasty operation. Further, out of these seven bilateral cases, three died within a fortnight of admission in hospital, another stayed for one month and two for three months only.

Out of the 19 active cases, 15 are still in the hospital. They are further analysed in Table 8.

TABLE 8. *Analysis of 15 Active Cases Still in Hospital.*

No.	Name.	Duration of stay in Hospital.	Temp. on Adm. Present Temp.	E.S.R. on Adm. Present E.S.R.	Change in Weight in Lbs.	Radiological.
M 1	P. K.	5 months.	97–100 F. 98–99 F.	34 Uncor. 26	Plus. 16.	Stationary.
M 6	P. D.	½ month.	97–98 F. 98–99 F.	23 18	Plus. 8.	Stationary.
M 2	K .K.	2½ months.	98–100 F. Afebrile.	32 16	Plus. 21.	Stationary.
M 7	D. R.	4½ months.	97–99 F. Afebrile.	20 Cor. 36	Plus. 1.	Deteriorat.
M 17	N.	10 months.	97–99 F. Afebrile.	55 Uncor. 36	Plus. 19.	Mod. Imp.
M 22	S. S. I.	10 months.	Afebrile. Afebrile.	48 Uncor. 8	Plus. 10.	Stationary.
M 21	V. N.	17 months.	98–102.4.F. Afebrile.	? 40	Plus. 13	Consid. Imp.
F 11	T. B.	7 months.	98–99 F. Afebrile.	40 40	Plus. 23.	Mod. Imp.
F 9	P. S.	3 months.	97·5.–99 F. Afebrile.	42 Uncor. 6	Plus. 17.	Mod. Imp.
F 6	S. B.	10 months.	98–102. 98–100.	? 6	Minus. 7.	Deteriorat.
F 5	I. B.	9 months.	98–102 F. 98–99.	57 Uncor. 40	Plus. 1.	Deteriorat.
F 17	M.	1½ month.	Afebrile. Afebrile.	44 40	Plus. 6.	Stationary.
F 15	S.	14½months.	97–99 F. Afebrile.	18 40	Plus. 42.	Consid. Imp.
F 14	K. B.	13 months.	98–100 F. Afebrile.	40 Uncor. 18	Plus. 30.	Deteriorat.
F 16	V. B.	17 months.	98–100 F. Afebrile.	84 36	Plus. 7.	Deteriorat.

Note : (1) that out of 15 active cases, all except 4 are afebrile. Amongst these 4 patients, 3 are running a temp. upto 99°F. and 1 upto 100°F

(2) E.S.R. is below 10 in 3, between 10-20 mm in another 3, between 20 and 30 in 1 and between 30 and 40 mm in 8 cases.

(3) Radiologically—as assessed independently of the clinical data by the radiologist (on comparing the first and last roentgenogram taken at the end of Jan. 1951)—5 cases have deteriorated, 5 are stationary, 3 are moderately improved and 2 are considerably improved.

(4) Since admission, only 1 has lost weight, 6 cases have gained weight between 1 to 10 lb , 4 between 11-20 lb. and 3 between 21 to 30 lb. and 1 case 42 lb.

DISCUSSION AND SUMMARY

64 percent of cases were bilateral on admission, 62 percent had involvement of equivalent of one lung or more, and 31 percent, about one third, came in category B3, *i.e.*, cases with profound systemic disturbance or constitutional deterioration and with marked impairment of function, either local or general,—cases which have a uniformly bad prognosis everywhere. This extent and severity of the disease was, inspite of the history being of a duration of 6 months or less, only 80 percent of cases. The only fallacy is that earlier symptoms might have been ignored by this hospital class of patients. This raises an important question : Is the disease more acute in this Province? Is it due to the soil prepared by poverty, wide-spread malnutrition, intercurrent infections like malaria and the young age group to which most of the patients belong, or to an especially virulent strain, or large frequent doses, possible only in such overcrowded conditions as are found here?

The high incidence of acute forms of disease is reflected in the form of collapse therapy for which they were found suitable. Only 11 cases were thought fit for A.P. and many of these received it only later in the course of the disease, while phrenic crush and P.P. were given to 15 cases.

It is apparent that streptomycin and P.A.S. should be used together in full dosage (16 to 20 Gm. daily) and full advantage should be taken of the effect of P.A.S. in the prevention of development of a streptomycin resistant strain. It is apparent that streptomycin alone can seldom cure pulmonary tuberculosis and its chief role should be in preparing cases for suitable collapse therapy (O'Conner[27] 1949, Streptomycin Committee of the Veterans Administration[31] 1950) or for controlling spreads and flare-ups. Further, it may be possible in combination with P.A.S. to give more than one course, preferably lasting a month or even less, stopping as soon as the desired end or "cooling off" of the lesion has been achieved.

Last of all, there is a very important question of making the best use of the limited hospital beds. Here, with 20 beds, in a period of 15 months, only 39 cases could be treated. There is a great urge for domiciliary treatment in England (Trenchard[33] 1949, Tattersal[34] 1949, Lancet[15]—1949) where the bed scarcity is not so acute as here and the home conditions and economic conditions are comparatively much better. Maclean and Gemil[19] (1948) published the results of 150 A.P. inductions in the outpatients in Glasgow. Macdonald[18] (1948) and Pritchard[28] (1948) writing about the results of Maclean advocated P.P. and phrenic crush for home treatment for cooling off active cases. Heller[10] (1949) published remarkably good results in consecutive inductions (150 P.P. and 50 A.P.) with a follow up of 2 years or more. The good results were attributed to the care taken in the selection of cases. Adequate provision for home care, reliable transport to convey patients to the chest clinic when required, the possibility of obtaining a chest physician's help at any time in emergencies and adequate facilities for adhesions section, were thought to be important. A recent annotation in Lancet[16] (1950), talking of poor dwelling conditions in Glasgow said that "domiciliary treatment can hardly hope to succeed in such conditions and protection of contacts becomes a mockery." Further "In over crowded cities we can only hope to check its (tubercle) widening course by providing more houses or more beds but preferably both." The Government of India Health Survey and Development Committee[9] (1945) considered this problem and thought that it was most acute in one room tenements and that free provision of dwellings for the patient and his family (where isolation may be practised) by the local health authorities was the only solution.

A better and larger use of the small number of available hospital beds could be made by combining a short stay in hospital essential for induction of collapse therapy and training of the patient and his family, with a follow up and continuation of collapse therapy in the outpatient department; but this will be only possible with much greater aid and interest by the local heath authorities in looking after the patient and his family in his home and carrying the hospital facilities to the home.

REFERENCES.

1. Barnwell, J. B. *et al*: The Effects of Streptomycin upon Pulmonary Tuberculosis, Amer. Rev. Tuber **46**: 485-605, 1947.
2. Bignall, J. R. *et al*: Intermittent Dosage in the Treatment of Pulmonary Tuberculosis with Streptomycin. A Report to the Streptomycin in Tuberculosis Committee of the Medical Research Council, B. M. J. **1**: 1224-1230, 1950.
3. Cartensen, B. and Andersen, K. L.: Resistance to P.A.S., Lancet **1**: 878, 1950.
4. Cayley, F. E. W.: Potassium Deficiency in P-amino Salicylic Acid Therapy, Cardiac and Paralytic Effects, Lancet **1**: 447-448, 1950.
5. Council on Pharmacy and Chemistry: The Effects of Streptomycin on Tuberculosis in Man-Preliminary Statement, J. A. M. A. **135**: 634-641, 1947.
6. Erdie, A.: P-amino Salicylic Acid in Tuberculosis, Lancet **2**: 118-119 1948.
7. Harris, W. C. and Walley, R. V.: Exfoliative Dermatitis Complicating Streptomycin Therapy, Lancet **1**: 112-114, 1950.
8. Heaf, F. and Rusby, N. L.: Recent Advances in Respiratory Tuberculosis,

pp. 250-253, J. & A. Churchill Ltd., London, 1948.
9. Health Survey and Development Committee: Report of the Health Survey and Development Committee, pp. 160 Vol. II, Delhi, Manager of Publications, Delhi, 1946.
10. Heller, R.: Domiciliary Collapse Treatment, Tubercle, Lond. **30**: 204-209, 1949.
11. Horne, N. W.: P. A. S. Lancet **1**: 979-980, 1950.
12. Lancet, : Streptomycin in Pulmonary Tuberculosis, Lancet **2**: 733-734, 1948.
13. Lancet.: A Less Toxic Streptomycin, Lancet **1**: 155-156, 1949, a.
14. Lancet.: Potentiation of Streptomycin, Lancet **1**: 31, 1949, b.
15. Lancet.: Home Management of Pthisis, Lancet **21**: 953, 1949, c.
16. Lancet.: Some Tuberculosis Figures, Lancet **1**: 39-40, 1951.
17. Livingstone, R.: The Remote Results of Collapse. Therapy in the Treatment of Pulmonary Tuberculosis, Tuberle, Lond. **30**: 79-85, 1949.
18. Macdonald, N.: Artificial Pneumothorax, Lancet **1**: 268, 1948.
19. Maclean, A. and Gemil, J. S.: Artificial Pneumothorax, Survey of 150 Inductions in Out-patients, Lancet **1**: 173-175, 1948.
20. Madigan, D. G. *et al*: Para-amino Salicylic Acid in Tuberculosis, Clinical and Pharmacological Aspects, Lancet **1**: 239-245, 1950.
21. Marshal, G.: Health and Tuberculosis Conference, Lancet **2**: 123-128, 1949.
22. Medical Research Council Committee for Clinical Trial of Streptomycin in Tuberculosis: Streptomycin Treatment of Pulmonary Tuberculosis, B.M.J. **2**: 769-782, 1948.
23. Mitchell, R. S.: Phrenic Nerve Interruption in the Treatment of Pulmonary Tuberculosis, II, Complications and Sequelæ of Phreniclasis, Am. Rev. Tuber. **60**: 168-182, 1949.
24. Nagley, M. M.: Scrotal Pneumocele and Inguinal Hernia Complicating Pneumoperitoneum Therapy Brit. J. Tuber. **40**: 17-20, 1948.
25. Nagley, M. M. and Logg. M. H.: Para-amino Salicylic Acid (P.A.S.) in Pulmonary Tuberculosis, Lancet **1**: 913-916, 1949.
26. Nagley, M. M.: Potassium Deficiency in P.-amino Salicylic Acid Therapy. Lancet **1**: 592, 1950.
27. O'Conner, J. B.: Integration of Streptomycin with Other Forms of Therapy for Pulmonary Tuberculosis, Amer. Rev. Tuber. **60**: 264-268, 1949.
28. Pritchard, E. K.: Artificial Pneumothorax, Lancet, **1**: 302, 1948.
29. Rogers, W. N. and Garrett, J. V.: Scrotal Pneumocele as a Transient Complication of Artificial Pneumoperitoneum, Brit. J. Tuber. **41**: 70-73, 1947.
30. Streptomycin Committee, Veteran's Administration.: Streptomycin in the Treatment of Tuberculosis, J. A. M. A. **138**: 594-593, 1948.
31. Streptomycin Committee of the Veterans Administration: Current Status of the Chemotherapy of Tuberculosis in Man. J.A.M.A. **124**: 650-653, 1950.
32. Streptomycin Sub-Committee of Standing Advisory Committee in Tuberculosis to the Ministry of Health (Great Britain): Streptomycin in the Treatment of Tuberculosis. An Official Memorandum, Lancet **1**: 273-275, 1949.
33. Trenchard, H. J.: The Tuberculosis Situation, Waiting Lists and Domiciliary Treatment, Lancet **2**: 956-957, 1949.
34. Tattersal, W. H.: The Home Treatment of Pulmonary Tuberculosis, Lancet **2**: 957-958, 1949.
35. Vallentin, G. *et al*: P.A.S. in Pulmonary Tuberculosis, Tubercle, Lond. **31**: 2-10, 1950.
36. Young, F. H.: The Place of A.P. in the Treatment of Pulmonary Tuberculosis Proc. R. Soc. Med. **42**: 244-46, 1949.

PROGRESS IN THERAPEUTICS: 1950

V. Iswariah *

Hopes and beliefs in the worth of drugs that characterise this decade, as against the 'Therapeutic Nihilism' of an earlier period continue, yet, several recent findings tend to confound the 'rational drug renaissance'. Competitive drugs are hurled today on the market or perhaps elegantly offered to medical men, pleasingly couched in colourful brochures. The puzzled medical man is expected not to prescribe any new therapeutic agent until he is first acquainted with studies that preceded the introduction of these compounds. From voluminous literature he has to sort the gold from the dross, the permanent from the evanescent.

The year under review in therapeutics has been overwhelmed by the new conception of diseases and their treatment. Selye and Hench seem to have set a forest on fire. Cortisone and A C T H are finding new and ever increasing, not to speak of strange applications. Their introduction is the outstanding event in the therapeutic world. It may be said that this is the greatest advance since the arrival of sulpha compounds and the antibiotics.

More data about the antibiotics, sulpha compounds and antihistaminics have been gathered during the past year about their extension or limitation in therapeutic application. One gets a distant view of the aridity to which antibiotics are likely to produce in the field of therapeutics. Organisms are proving superior to man in succeeding to resist his weapons. "They are not taking the present widespread attack on them lying down : some are defending themselves very effectively and some are even turning out weapons to their own advantage." L. P. Garrod (1951)[4]. This is indeed a note of discord in an otherwise pleasant prospect.

CORTISONE & A C T H

In the earlier reports on Cortisone and A C T H in rheumatoid arthritis, the jubilation over the spectacular effect made all concerned lose sight of the "Comprehensive Principle" underlying the novel treatment. The propounders of the hypothesis were not to blame, but the subsequent application of the two compounds to diverse ailments awakened the necessary interest in the medical world to study and grasp the significance. It is fascinating to note that Hench and Kendal[6] embarked on their voyage of discovery almost at the same time as Selye ; they seem to have met in a lonesome island.

---

* Department of Pharmacology, Madras and Stanley Medical Colleges.

The Conception :—As a result of animal experiments over an extensive period, Selye an experimental surgeon had suggested that infection, intoxication, trauma and emotional tension which he designated "stress" make the body respond by its hormonal output and adjustment. The hormones tend to raise the resistance of the body to the onslaught of stress. Stress provokes an "alarm reaction", a stage of resistance and a stage of exhaustion, all of these embracing the "General Adaptation Syndrome". Defence and damage are both involved in the reaction. The succession of events may be rapid and fulminant or delayed and protracted. The reaction is mediated by glucocorticoids and an unknown factor. This conditioning factor and the target organ determine the nature of the disease like nephrosclerosis, periarteritis nodosa, rheumatoid arthritis, peptic ulcer, hypertension-allergy, etc. If the stress response mechanism is normal, repair or healing is effected. If upset it gives rise to diseases of adaptation or adaptation syndromes.

The hormonal response is mainly from the pituitary and from thence the suprarenal. In a perfectly adapted case, the stress provokes the pituitary to secrete A C T H or adrenocorticotrophic hormone with diminished secretion of its other hormones. This in turn provokes the suprarenal cortex to secrete (1) the glucocorticoids to which belong cortisone and compound F, causing gluconeogenesis, lymphopænia, involution of lymph glands, granulocytosis or increased phagocytosis and antibody formation. They tend to lower the sedimentation rate by their effect on blood protein. Then comes (2) the mineralo-corticoids to which belongs desoxycorticosterone or deoxycortisone, that tends to antagonise glucocorticoids, cause retention of sodium chloride and water and eliminates potassium, produces hyalinisation of glomeruli and nephrosclerosis, releasing pressor substances. In experimental animals Selye found an increase of glucocorticoids and a decrease of mineralocorticoids after stress, the former increasing while the latter reducing resistance to stress or traumatic shock. Pure A C T H is predominantly glucocorticotrophic. The crux of the problem is what determines the secretion of the right corticoid, for if there is a disproportion or over production of mineralocorticoids, disease results. The many changes that organs undergo during the reaction to stress may eventually lead to diseases of adaptation.

A strange observation had been made earlier that pregnancy and jaundice acted as stress or agents to provoke cortisone endogenously to alleviate pre-existing diseases.

Objection to this conception was raised by some experimentists as desoxycorticosterone is not a naturally occurring hormone. Selye has replied by injecting a naturally occurring corticoid *i.e.* 11 deoxycortisone and produced results similar to desoxycorticosterone. (Details of the hypothesis could be had from Lancet—Editorial Feb. 3 1951 p. 277.)

Therapy :—Cortisone and A C T H are frequently used as though they were synonyms. Many ailments are treated with either of the two with perhaps similar results. But it should not be forgotten that A C T H or the corticotrophic hormone may stimulate in addition to the wanted glucocorticoids, other unwanted corticoids. Pure A C TH is said to stimulate only the glucocorticoids. However, side effects are more to be expected with A C TH therapy than with cortisone therapy.

A host of diseases in addition to rheumatoid arthritis are said to respond to cortisone or A C T H therapy. The following list may not be quite exhaustive. It includes chorea, gout, other collagen diseases, ulcerative colitis, lupus, disseminated scleroderma, etc. which are said to respond very favourably. The next series said to respond favourably include asthma; overt allergies, like atopic dermatitis, glomerulonephritis; neoplastic diseases like carcinoma, Hodgkin's disease, chronic myeloid and lymphoid, leukæmias; infectious diseases like pneumococcal and virus pneumonia, poliomyelitis, etc., other chronic ailments like hepatitis, herpes, pemphigus; diseases of the nervous system like amyotrophic lateral sclerosis, disseminated sclerosis, myasthenia, psychosis, hyperthyroidism, hyper or hypoglycemias, etc. Asthma and hay fever are said to respond better to cortisone than to the antihistaminics.

(This list defies analysis on any basis. A more comprehensive list could be had from B. M. J. June 17-1950 p. 1383).

Mayo clinic reports (1950) [12] that many surgical operations could be performed with safety under a 'cortisone umbrella' like glaucoma, uveitis. etc. We have heard of the sulpha or antibiotic umbrella used by surgeons and today we hear of a 'non disinfected umbrella'.

In other words, the disorders listed above are of adaptation or breakdown in the mechanism of the pituitary—suprarenal reflex and deficient output of the required hormone. Is cortisone therapy than a mere substitution or replacement therapy? While 10-20 mg. of cortisone daily can maintain a patient with complete adrenal deficiency, 100 mg. daily is needed to change the course of rheumatoid arthritis. Is it then an imbalance between gluco and mineralocorticoids or is it a general disturbance of steroid metabolism in the body? It has been shown that in rheumatoid arthritis, progesterone is not well metabolised. Hench (1950) [6] said that the hormone did not kill any microorganism or remove any unknown irritant. What it did was to provide susceptible tissue with a shield-like buffer. It did not put out the fire, nor repair the damage, but it did provide a kind of "asbestos suit" by which the patient was protected. When the suit was removed prematurely, the tissues were again subjected to the flame. But once the inflammation was suppressed, it could remain suppressed by simple maintenance dose.

In general, A C T H and cortisone act in a legion of diseases through changes in enzyme system. This view has been corroborated by the study of A C TH on the excretion of uropepsin. A marked increase in excretion of uropepsin is noticed after an injection of A C T H. A functioning gastric gland seems to be necessary for this response. Patients with adrenal insufficiency do not excrete uropepsin after A C T H, but administration of cortisone promotes the excretion. An allied type of treatment for rheumatoid arthritis was to stimulate endogenous adrenocortical activity by induction of hypoglycemia by insulin or electric convulsions. Clinical improvement with both are accorded by Kersley (1950)[10] with evidence of a direct stimulation of adrenal cortex for more cortisone output. It is also possible that there is a synergistic action between insulin and endogenous cortisone (*vide infra*).

Hazards :—The dangers attending on this form of therapy are not to be lost sight of. A C T H may give rise to defects in healing by granulation, a rise in blood pressure sometimes endangering life in hyperpietics, mental changes and sometimes precipitating Cushing's syndrome. It has been shown fairly definitely that in tuberculous conditions of the lung or joint or larynx, more often than not there is a deterioration in the general condition. This unfortunately may follow initial hopes of improvement. Inclusion of streptomycin or para-amino-salicylic acid did not alter the course favourably. The hope once entertained that cortisone by its fibrolysis may bring the antituberculosis drug nearer the target was blasted by defects of macrophage activity, lowering of resistance and increase in cavitation. Individual tolerance to cortisone and A C T H seem to vary widely. It is said that males as a rule tolerated the hormones better than females. Minor side-effects were restlessness, insomnia and alteration in psyche. Hypertrichosis, folliculitis, retention of fluids and amenorrhœa were noticed. A retrocervical hump (buffalo hump) was noticed in some. A few cases of spontaneous fracture in elderly osteoporotic patients are also recorded. To prevent adverse effects it is suggested that after initial suppressive doses, only the smallest effective maintenance doses should be tried.

Cortisone is now found effective by mouth. No larger amounts than the intramuscular doses are necessary, as absorption is quite satisfactory. A sample of A C T H has been prepared from a whale found in Norwegian waters and is now available for oral use.

Cortisone and Malignancy :—Squamous celled carcinoma, acute leukæmias and lymphosarcoma were given cortisone or A C T H. Spies (1950) [14] obtained very encouraging results with relief of pain in carcinoma, reduction in cells in leukæmias and reduction in size of lymph nodes in lymphosarcoma. It looks as though vital changes are brought about in malignancy by these agents. The chemical condition of the body was somehow changed by cortisone and A C T H to arrest the activity of the malignant elements.

Caution in acceptance :—The unfolding of the creed of Selye coincided with the discovery by Hench and Kendall helped by Reichstein [6], of Cortisone and A C T H in rheumatoid arthritis. One is not sure here as to who influenced the other—Hench and Kendall having embarked on their journey at the same time as Selye. (The Nobel prize has been awarded to Hench, Kendall and Reichstein.) Selye himself has said that it will take many years, indeed many generations, before the details of the general adaptation syndrome are satisfactorily elucidated. Is the general adaptation syndrome a mere vapour or the new creed in medicine? Is mechanistic or materialistic science drifting to the vitalism of a bygone age? A theory that apparently gives satisfactory or consoling explanations of many ills, nay any ill, may be the beginning of the reversal of progress, or the reversion to the dark ages. The deductive science of Galen had to be purged by the inductive method of the renaissance. Let us therefore be on our guard against the threat of a new dark age, this time dressed up in all the embroidery of science and not of religion.

(It is learnt that Selye has published a book called "Stress"—1950 £5-5).

ANTIBIOTICS

Oral Penicillin :—A fascinating oral penicillin compound is now on the market. It is a buffered calcium crystalline procaine penicillin flavoured with chocolate. A teaspoon of it contains 50,000 units which may be given three hourly with milk or water. One has to remember that blood concentration of penicillin by the oral route is about 20-25 percent of the same given parenterally. And yet the oral route is gaining ground and intravenous route receding.

Penicillin in Syphilis :—Jeffries *et al*[9] (1951) in a large series of cases tried 500,000 units of penicillin in a peanut oil bees wax suspension, daily for 8 days, followed by a short course of arsenic and bismuth. This treatment was compared with penicillin and with bismuth alone (excluding arsenic), bismuth being given upto a total of 4 Gm. in divided doses every four days. Treatment with penicillin and bismuth was quite as satisfactory as with arsenic, with the added advantage of freedom from arsenical toxicity. It looks as though the arsenical era in the treatment of syphilis is coming to an end.

Penicillin has been found effective in Weil's disease though aureomycin is deemed superior.

Penicillin in Neurosyphilis :—Comparison of the effect of penicillin alone and with penicillin combined with pyrexial therapy in neurosyphilis seems to indicate that penicillin alone gives as good or even better results than the combined therapy.

Penicillin is said to appear in the C.S.F. two hours after an intravenous dose of 500,000 units. The use of caronamid increases the diffusion of penicillin into the C.S.F. Higher concentrations may be reached in patients with meningitis. This method is claimed to be superior to intrathecal medication which carried with it greater hazard.

Reactions to Penicillin—Penicillin is beginning to show its unseemly aspect. Reactions are reported not infrequently—sensitiveness and sometimes anaphylactic reactions. Before crystalline penicillin came into use, reactions were attributed to impurities in the amorphous form, but cases of reactions are being reported after crystalline penicillin administration. Some try to explain this as being due to previous sensitisation to fungi allergically similar to *penicillin notatum*, but evidence is not lacking to show that penicillin itself acts as a sensitising agent. Urticaria is a frequent side reaction, immediate or a fortnight after completion of treatment. A pompholyx type of reaction is also noticed. Strangely many fungous infections are aggravated by penicillin. The topical application sometimes causes vesicular eruption and sometimes sensitises the patient to penicillin very much like the topical application of sulpha compounds. Sometimes laryngeal œdema and asthma-like symptoms were noticed. In late syphilis, herxheimer-like reactions may be noticed especially in meningeal or meningovascular syphilis and in interstitial keratitis. It looks as though the procaine penicillin compounds in oil produce the least number of reactions and in least number, while aqueous penicillin compounds in high doses such as 500,000 units give the maximum reactions, say, in about 7-10 per cent of cases so treated with massive doses.

Synergism and Antagonism in Antibiotics—It is an axiom that two or more chemotherapeutic agents acting together may produce effects better than any one, as in the treatment of malaria, syphilis, amœbiasis etc. The sulpha compounds and penicillin were found effective in combination in some diseases. If two drugs interfere with the same stage in a metabolic cycle of an organism, their combined effect may be expected to be additive. If there are different modes of attack, the organism surviving the attack of one is exposed to that of the second, when the two attacking agents are said to be synergistic. The combination of drugs tend always to minimise the chances of organisms developing resistance, as exemplified in streptomycin and P.A.S. or penicillin and streptomycin, in subacute bacterial endocarditis. The incomplete bactericidal action of penicillin on enterococci is said to be perfected by the addition of streptomycin. There is also some indication that penicillin, streptomycin and the sulpha compounds control infections by *H. influenzæ*, better.

On the other hand, is it possible that one drug without aiding another, interferes with its action? In mice infested with *Streptococcus pyogenes*, the mortality after treatment with penicillin and chloramphenicol was three times that after treatment with penicillin alone. Other similar observations seem to suggest that antibiotic 'shot gun therapy' may sometimes misfire and defeat the object. A bacteriostatic agent if combined with a bacteriocidal agent of the penicillin type, may not always have an additive or synergistic effect. Penicillin and streptomycin are bactericidal while chloramphenicol and aureomycin are bacteriostatic, to be more correct, growth restraining or bacteriofrenic. There is therefore a real possibility of either of the two latter interfering with the therapeutic activity of either of the two former, *i.e.*, penicillin and streptomycin.

Streptomycin : *Present Status* :—The Council of Pharmacy and Chemistry of the American Medical Association and the Medical Research Council of Britain have independently summarised the present position of Streptomycin. (1) Reduction of the daily dosage from 2 Gm. to 1 Gm. has given satisfactory results therapeutically and in eliminating toxic possibilities. Toxicity is more due to sustained blood plasma concentration rather than to occasional peaks. (2) In tuberculosis, streptomycin may be tried for acute life threatening cases ; for all others, non streptomycin treatment is to be advocated. In tubercular meningitis and acute miliary forms, streptomycin may be mandatory, but its value intrathecally is much disputed. Hopes of controlling tubercular empyema are remote. (3) Combined with P.A.S. 20 Gm. a day, 1 Gm. of streptomycin a day considerably reduces the risk of development of resistant organisms. Whether smaller doses of P.A.S. should suffice for satisfactory treatment, is still a subject of investigation. (A chemical compound pairing streptomycin with P.A.S. is now available). (4) Promizole with streptomycin is also said to be of value in the treatment of miliary tuberculosis and tubercular meningitis. Synergism is in evidence, but whether the combination could prevent the development of resistant organisms is doubted. (5) In combination with calciferol, streptomycin has been found effective in the treatment of lupus vulgaris. Cutaneous sinuses and fistulæ also gave a satisfactory response. Slow but appreciable improvement is also noticed in bone and joint tuberculosis. (6) In tuberculosis of the genito-urinary tract and alimentary tract, streptomycin has yielded varying results. The American school however favours its use. (7) The efficacy of streptomycin in granuloma inguinale remains undisputed. 1 Gm. three times a day followed by 1 Gm. a day for five days gave good results as gauged by the non relapse for a period of two years. (8) Gonorrhœa and chancroid also respond to streptomycin, but to rush to streptomycin before penicillin, is inadvisable, unless it is to eliminate subjacent treponemal infection. In America it is said that gonococci are already sulpha fast ; possibly elsewhere too. Let them not now become streptomycin fast as well. Chancroid, resistant to sulpha drugs, also yields to streptomycin.

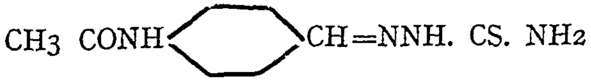
(9) The claim of streptomycin to be the drug of choice in plague has not been challenged so far (except by statisticians.)

OTHER CHEMOTHERAPEUTIC AGENTS IN TUBERCULOSIS

Streptomycin was hailed not so long ago as a boon to tuberculosis, but the scope and utility of antibiotics are constantly changing. The battle royal between micro-organism and the attacking weapon will never be static and it is hard to predict the winner. What is happening with penicillin and streptomycin may be seen in other spheres; the present series of antibiotics may ere long be rendered useless and create a continued search for newer ones. And so the study of other chemotherapeutic agents in tuberculosis goes unimpeded.

P.A.S. :—This is deemed today as an indispensable adjunct in the treatment of tuberculosis. The Medical Research Council of Britain has reached the following tentative conclusions. Some of the conclusions overlap those already mentioned with reference to streptomycin. Patients receiving streptomycin alone, compared to those receiving P.A.S. alone for tuberculosis, revealed the superiority of streptomycin as evidenced by (*a*) earlier radiological improvement (*b*) earlier sputum clearance and (*c*) general improvement. In the combined treatment, clinical improvement was more evident and the sedimentation rate fell more rapidly than in either of the two earlier groups. The main function of P.A.S. seems to be to maintain the therapeutic utility of streptomycin for a longer period. Doses of 12 Gm. of P.A.S. daily with 1 Gm. streptomycin every other day, or even every third day was deemed a satisfactory schedule. Among 700 patients so treated, resistant organisms were nil after four months. While streptomycin treatment can be intermittent, P.A.S. treatment has to be continuous. For, when both drugs were given every third day, cases became bacilli resistant in three months. In the treatment of early cases ,P.A.S. has to be preferred to streptomycin, streptomycin being reserved for a more serious crisis in tuberculosis, whether for an acute exacerbation or in preparation for an operation. "To use it indiscriminately is to throw away a trump card needed at a later stage".

Thiosemicarbazones :—About ten thiosemicarbazones exist, of which only a few are active against tuberculosis-like thiacetozone or contaben or berculon B thioparamizone, seroden, etc.



These compounds promised to be a valuable aid to streptomycin in the treatment of tuberculosis. Tuberculosis of bone, intestine and bladder respond satisfactorily to this. In experimental tuberculosis in mice, results with thiosemicarbazones compared very favourably with P.A.S., but are inferior to streptomycin. In doses of 20-50 mg. daily for two weeks or more, gradually increased to 200 mg. a day, if patients could tolerate them for 6-12 months, the results were good in fresh exudative types, rarely in laryngeal and intestinal tuberculosis. But with the above schedule the drug invariably showed, toxic reactions which are deemed much worse than those with streptomycin. The toxic reactions have been compared to those of arsenicals in the prolonged treatment of syphilis. Minor toxic reactions are anorexia, malaise, headache, vomiting, etc. More serious ones are anæmia, agranulocytosis, severe conjunctivitis, cerebral œdema and jaundice. Though there is a fall in the erythrocyte sedimentation rate and increase in gama globulin, they dont seem to be pathognomonic of real improvement. On a final analysis after sufficient clinical trials, despite enthusiasm in Germany, thiosemicarbazones cannot be deemed equal to streptomycin or P.A.S. as claimed earlier. They are however of value in leprosy (*vide infra*).

LEPROSY

It looks as though the discarded drugs in tuberculosis are given scope in leprosy. In 1939, promin that was hailed for tuberculosis was found to have good effects in leprosy in 2—4 Gm. doses intravenously. In 1944 came diasone, the advantage being that it was active orally and less toxic than promin. Then came sulphetrone or 4.4 biphenyl propyl amino diphenyl sulphone tetra sodium sulphonate. The parent diamino diphenyl sulphone is now preferred like the parent sulphanilamide after prontosil and proseptasin. D A D P S is deemed the cheapest for mass treatment and can be given in 100 mg. doses daily, orally, for two weeks, followed by 200 mg. daily for another two weeks. This dosage may be on the excess side for Indian conditions. Treatment for a month or more may cause anæmia due to hæmolysis or interference with absorption of essential hæmatinics. Dermatitis and rarely psychosis are also possible.

The thiosemicarbazones are also found to be effective in leprosy. Preliminary reports claim that the thiosemicarbazones in leprosy have reduced the death rate, due to cachexia, bronchial obstruction, renal amyloidosis, etc. Ulcers and nodules heal rapidly, bacilli disappear; certainly a new era has been inaugurated in leprosy treatment.

Promacetin is another recent compound of use in leprosy. The cost of D A D P S for treating a patient according to the above dosage, which is certainly not absolute, works to about Rs. 8 per patient.)

CHLORAMPHENICOL

The use of chloromycetin or the synthetic chloramphenicol has been established more clearly during the past year. The Ministry of Health in the U.K. has given a provisional list of diseases where it is indicated with good, satisfactory or indifferent results. (1) Infections where chloramphenicol is superior to penicillin or sulpha drugs are typhoid, paratyphoid (excluding carriers), brucellosis, rickettsial diseases like typhus, Q fever, virus diseases like psittacosis, lymphogranuloma, atypical virus pneumonia, resistant urinary tract infections due to *E coli*, *B proteus*, *B. pyocyaneus* and *Streptococcus fæcalis.* (2) Infections where results are satisfactory but not fully substantiated, *e.g.*, whooping cough (*vide infra*), *Salmonella* infections, *H. influenzae* meningitis, etc. (3) Infections where chloramphenicol is not likely to be superior to others or of any value, *e.g.* influenza, poliomyelitis, tuberculosis, syphilis, ulcerative colitis and the virus cold.

A specific effect on typhoid organism could be claimed with the proviso that about 50 mg. per Kg. as the initial loading dose, followed by 0.25 Gm. at intervals of three hours for about 2-3 days, brings down fever and toxæmia. It is advisable to continue treatment for about 5 days after the temperature has come down to normal. An average aggregate dose of 20-25 Gm. for 8-10 days should suffice in most cases. Urine, stool and blood cultures are satisfactorily negatived by chloramphenicol by this method, but relapses are not infrequent and it is not evident now if this is due to inadequate dosage or too early cessation of treatment. So far the organisms do not show refractoriness during relapses. The return to normal of the temperature should not make the physician relax general supportive treatment. Fatal hæmorrhage during the quiescent period, *i.e.*, 3-7 days after the temperature had touched normal are reported. Intestinal lesions do not heal as promptly as the toxæmia is controlled and so it is advisable to be on guard against hæmorrhage or perforation specially after the fever has been controlled. On the whole, results with chloramphenicol in typhoid are encouraging, if the drug is used before the tenth day of fever.

Chloramphenicol in Pertussis—Since the supply of chloramphenicol improved during the past year, its utility in pertussis is gaining ground About 2 Gm. were needed for children aged 1—2 years with increasing doses for advancing years. About 0.25 Gm. of chloramphenicol by mouth twice or thrice a day is administered; sometimes children have difficulty in swallowing the capsule and it should also be remembered that the stuff is very bitter if the child bites the capsule. In those cases it was possible to administer chloramphenicol as a suppository, very rarely, was it given intravenously in propylene glycol. With this scheme of treatment, fever, if present, usually subsides in about 2 days, paroxysms of cough in 4-6 days and the results are altogether cheering. Reports from S. India have been encouraging.

Chloramphenicol in Cholera—Here, unlike typhoid, chloramphenicol clears the stool of cholera vibrio, but the clinical condition does not seem to improve satisfactorily. Once the symptoms of dehydration have set in, chloramphenicol is not of much value; the old, time honoured methods of treating dehydration are to be resorted to. Possibly chloramphenicol may find a place as a prophylactic in cholera.

AUREOMYCIN

In 1949, the Ministry of Health in U. K. restricted the use of aureomycin to (1) brucellosis (2) lymphogranuloma (3) proved cases of virus pneumonia and (4) ornithosis, a virus infection of birds.

In the previous review of "Progress in Therapeutics-1949" published in this journal (May 1950 p. 224) about fifteen conditions were listed as being amenable to aureomycin therapy. The practising medical man knowing that different organisms affect different systems or that the same organisms affect different organs of the body, should intelligently use the knowledge regarding sulpha compounds, penicillin, streptomycin, aureomycin, etc., as their effects often overlap. Combined oral and intravenous aureomycin is generally indicated only in severe infections. Orally, aureomycin may cause nausea, vomiting, looseness of bowels, etc., to a worse extent than chloramphenicol. Disturbances of alimentary functions when aureomycin is administered over a prolonged period, make vitamin administration a rational necessity. A few patients after aureomycin showed strange symptoms of euphoria. It looks as though the blood level of aureomycin is not an accurate guide to its therapeutic potency. Aureomycin hydrochloride is stable in dry crystalline form and loses its activity rapidly on dilution, unless kept in neutral or slightly alkaline solution below freezing point.

An overall survey seems to suggest that aureomycin is less active than penicillin against most Gram-positive and Gram-negative cocci, and as effective as streptomycin against most Gram-negative bacilli. Fortunately, no inactivitating enzyme corresponding to penicillin has been isolated, nor are any highly resistant variants known to develop so far. It is hoped that this is not a mere provisional assessment.

The indications for aureomycin in the light of recent data may be summarised. (1) Aureomycin today seems to be the best, if not the first, effective agent against brucellosis in general. It is more effective against *Br. melitensis* than in *Br. abortus* or *Br. suis*. An aggregate of 4—6 divided as 0.5 Gm. doses every 6 hours on the first day and gradual and subsequent decrease, seem to be satisfactory. Aureomycin is here deemed superior to sulphadiazine-streptomycin combinations. It is thought that aureomycin-dihydrostreptomycin combination provides best results. (2) In penicillin and streptomycin resistant strains of staphylococci, aureomycin finds a useful place as in staphylococcal osteomyelitis, septicæmia, mastoiditis, severe carbuncle, etc. (3) Virus diseases like lymphogranuloma, atypical pneumonia and psittacosis, respond well. In a sense, aureomycin is a "specific" against all pneumonias. (4) Urinary tract infections with *B. proteus*, *B. Pyocyaneus* do not seem to respond to aureomycin, but combination with streptomycin seems to be more helpful. Aureomycin is active in acid urine. (5) Influenza with lung manifestations, from the sputum of which hæmolytic streptococci, staphylococci or *H. influenzae* or Friedlander's bacillus are recovered, respond fairly well to aureomycin. Aureomycin however has no effect on the virus of common colds.

TERRAMYCIN

Of the several recent antibiotics, terramycin announced in 1950 seems to have an assured future. From *Steptomyces rimosus*, terramycin is an amphoteric substance, the sodium salt having an alkaline reaction while the hydrochloride is acidic. Unlike aureomycin, which it resembles to some extent, the hydrochloride of terramycin is comparatively stable. Both salts and the parent substance are bacteriologically active. The hydrochloride is generally given by mouth in capsules 2 to 4 Gm. daily. The compound needs to be given six hourly as the optimum concentration falls after that period. It looks as though there is a limit to its absorption, as larger doses do not appreciably increase the blood concentration. Much of the drug remains in the bowel exerting a suppressive action on the intestinal flora. The C.S.F. concentration is not comparable to aureomycin. It reaches bile in fairly high concentrations. In a general sense, one may say that in equal or comparable doses, terramycin occupies an intermediate place between chloromycetin and aureomycin for blood concentration, chloromycetin reaching the highest concentration. Urine concentration however seems to be higher with terramycin.

Regarding its utility, it resembles aureomycin in exerting a lethal or inhibitory action on a wide range of organisms. However, the organisms of tuberculosis, *B. proteus*, *B. pyocyaneous*, *E. typhi* and such others, seem to resist its attack.

Therapeutically, terramycin could be used in (1) pneumonia including the virus variety (2) septicæmias (3) urinary tract infections (4) brucellosis (5) pertussis (6) rickettsias where it is counted equal to or even superior to chloromycetin and aureomycin and (7) possibly amœbiasis.

Lately, terramycin has been found effective in four of the venereal diseases including syphilis, lymphogranuloma, gonorrhœa and granuloma inguinale. Attempts to treat syphilis by giving 60 mg. per Kg. doses every 6 hours for 8 days, revealed that treponema disappeared (apparently though) from 2—4 days and the Wassermann Reaction was negatived in about a month.

Terramycin is not altogether free from side effects. Children treated for whooping cough felt nausea, often experienced abdominal pain, headache, vomiting, which symptoms stopped when the drug was discontinued. We may say that terramycin is a new antibiotic looked forward to with hope.

NEOMYCIN

Neomycin is earlier than terramycin and was thought to be a non-toxic substitute for streptomycin. It was also thought to be effective against streptomycin resistant tubercular organisms. Unfortunately all antibotics effective against tuberculosis are also found to be toxic.

Neomycin is from *Streptomyces fradiæ* : another antibiotic, fradicin, from the same was found to be effective against fungi and not bacteria. Neomycin so far is found active against 52 species of pathogenic organisms including mycobacteriæ, the enteric-dysenteric group of organisms, Friedlander's bacillus, *H. influenzæ*, *B. proteus*, *psuedolmonas* and presumably *B. pyocyaneus*. This is perhaps the first antibiotic active against *B. proteus* and *B. pyocyaneus* (confirmation awaited). We are mainly interested in neomycin for the reason that resistant tuberculosis' organisms are said to remain sensitive to neomycin. Resistance, if any, for neomycin is of the penicillin type, *i.e.*, slow and gradual. These hopeful data are set against the uncertainty of neomycin regarding its toxicity. Kidney damage has been noticed when tuberculous patients were treated with neomycin. Neomycin therefore remains "sub judice" in the year of grace 1950.

VIOMYCIN

A more recent antibiotic named Viomycin from *Steptomyces puniceus* is reported. Its mycelium is purplish red in colour—hence its name. It is a strong organic base and forms neutral salts. The sulphate and oxalate have been prepared in crystalline form, soluble in water and stable at room temperature at a pH of 5-6. It is said to be very active against all acid fast organisms. In mice infected with *M. tuberculosis*, viomycin conferred immunity to 90 per cent as against a 90 per cent death rate in untreated cases. (Amer. Jl. Tub. Jan. 1951 p. 3.)

SULPHONAMIDES

Nisulphazole or 2 p—nitrobenzene sulphonamide thiazole claims to be superior to the other non-absorbable compounds of the sulpha-guanidine, suxidine and pthalidine series. *In vitro* tests suggest the activity against dysenteric group, salmonella, paratyphosus and other infections. The activity seems to be due to a combination of sulphathiazole and nitro compound or some intermediate reduction compound. *Gantrisin* or 3.4 dimethyl 5 sulphanilamide isoxozole is a very soluble compound with minimal renal complications. Over 70 percent of gantrisin is excreted in a pure form and perhaps the rest is conjugated. The C.S.F. level is about a third of the blood level. This compound should therefore be of great value in patients where renal complications are to be guarded against.

Elkosin or 6 p amino benzene sulphonamide 2, 4 dimethyl pyramidine is said to be tolerated well when used for a prolonged period. It is also excreted in the urine mainly unchanged and very little is conjugated. Children treated for meningitis are said to tolerate the drug well.

Sulpha combinations :—The principle of sulpha combination therapy is accepted; there is no reason therefore for scramble amongst manufacturers for claiming a good or the best combination by permutating frequently. The old sulphatriad, *i.e.*, sulpha thiazole, diazine and merazine, after considerable use is not deemed inferior to other combinations such as sulphadiazine, merazine and pyrazine or sulphadiazine, merazine, and sulphacetamide. Sometimes the triad is increased to four. It is evident that sulphadiazine and sulphamerazine qualify for place in any mixture more than the others. The prejudice against sulphathiazole of late seems to be unfounded, unless there is a change in the composition of some brands.

The danger of sensitisation from combined partial doses of more than two sulpha compounds is much less than if an equal amount of any one compound is used.

ANTIMALARIALS

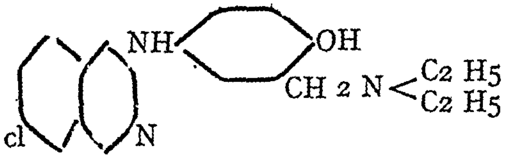
The W H O experts committee[16] on malaria is of the view that no antimalarial drug has all the desired qualities. The ideal antimalarial is one which is (1) a casual prophylaxis against all species of human malarial parasites (2) definite in its suppressive effect and that too rapidly and (3) of low toxicity and cheap. The efficacy of these drugs is by no means the same all the world over, which seems to suggest that different strains of parasites differ in their response to prophylaxis and therapy.

As a suppressive, chloroquine seems to hold the first rank so far, specially against *P. vivax*. In 1 Gm. doses followed after 8 hours by 0.5 Gm. and then 0.5 Gm. a day on two subsequent days, paroxysms of fever of all types are effectively controlled. If continued for six months with a weekly dose of 0.25 Gm., infection, especially of *P. vivax* seems to be eliminated.

To terminate an attack, proguanil or paludrine is slower than quinine, mepacrine or chloroquine, and so cannot be relied on in emergencies when given alone. The worst sequel to proguanil seems to be that the parasites tend to get resistant. Resistance is said to be on the increase in W. Africa. Resistance is likely to develop when relatively heavy infections are exposed to doses with sublethal effects. In the treatment of malaria either a 'sledge hammer' hit is to be delivered by careful dosage and a regulated course or 'polychemotherapy' is to be tried.

Camoquin :—This is a recent variant of chloroquine, *i.e.*, 4

(3-diethyl amino methyl-4 hydroxy anilino) chloroquinoline dihydrochloride dihydrate.



It is a yellow crystalline powder, soluble 1 in 5 in water, supplied as 0.2 Gm. tablets. Camoquin is said to be several times as active as quinacrine (mepacrine) against avian malaria. It is rapidly absorbed orally but rather vague in its distribution in body tissues. It is less toxic than quinacrine when used for a prolonged period. The dose advocated is 0.4 to 0.6 Gm., *i.e.*, 2 to 3 tablets, though in some regions like Brazil and Bolivia as much as 1 Gm. in single doses was necessary. It is claimed that a single dose (10 mg. per Kg.) produces more favourable results than divided doses. This single dose is claimed to give an early clinical cure and reduces the relapse rate; the effect being better than 0.3 Gm, thrice a day for 6 days or 1 Gm. every 6 hours for 24 hours. Parasites disappear in 36 hours (vivax) and 30 hours (falciparum) respectively.

When continued for 4 weeks with a daily dose of 0.1 to 0.2 Gm. there were symptoms of general weakness, uneasiness in the epigastrium, loss of appetite and occasionally insomnia. Such a prolonged treatment is never thought necessary. Confirmation of the above is awaited from observers in this country.

AMOEBIASIS

Chloroquine seems to be gaining ground as an effective amœbicide. Hepatic and pleural amœbiasis respond favourably to a 10 day treatment with chloroquine in a daily dose of 0.6 Gm. for two days and 0.3 Gm. for a subsequent week. It is surmised that the efficacy of chloroquine in purulent fluids is due to (at least partly) the high concentrations of the drug in a large number of leucocytes. The effectiveness of chloroquine as against the ineffectiveness of iodohydroxyquinolines like enterovioform and diiodoquine in extra intestinal amœbiasis, raises the doubt if iodine or the quinoline nucleus common to both is the effective component. In intestinal amœbiasis chloroquine is less effective. However, chloroquine seems to free us from emetine toxicity on the heart.

Aureomycin continues to give satisfactory results in amœbiasis of the gut. The high blood level obtained with aureomycin also holds hope for extra-intestinal amœbiasis as well.

Bacitracin, an earlier antibiotic that was used topically in pyogenic infections of the skin is reported to have satisfactory amœbicidal effect. In some cases, bacitracin eradicated intestinal amœbiasis that resisted aureomycin. About 80,000 units daily for about 10 days are recommended by oral route. Toxicity seems negligible so far. The disappearance of enterococci and claustridium during bacitracin therapy of intestinal amœbiasis seems to suggest the relation between these organisms and the pathogenesis of amœbic colitis.

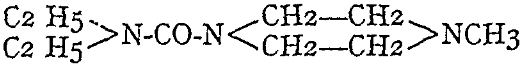
Filariasis

Hetrazan :—Reports continue to be satisfactory on the efficacy of hetrazan in clearing the blood of microfilaria. Evidence of destruction of parent worm is still circumstantial. Doses of 0.2 to 2 mg. per Kg. three times a day for 4 to 6 weeks seems to clear the peripheral blood of microfilaria. Negative blood counts appear in about 3-6 days from the start of treatment. *W. Bancrofti, loa loa,* and *onchocercus* all respond favourably. In onchocerciasis the effect is less rapid and less permanent compared to bancrofti infections.

According to some, hetrazan hydrochloride is better tolerated than hetrazan hydrogen citrate.

Hetrazan has also been found effective in creeping eruptions thereby revealing a larvicidal effect. Hetrazan was also found effective in ascariasis in 6 mg. per Kg. doses, thrice a day, for a week. Round worms were expelled without the aid of a purgative. One feels that this is too costly a treatment to be attempted for ascariasis.

Banocide :—*a new antifilarial agent.* This is a British rival for hetrazan called also diethyl carbamazine. It is 1 diethyl carbamyl-4 methyl piperazine citrate with the following structure.



$$\begin{matrix}C_2H_5\\C_2H_5\end{matrix}>\text{N-CO-N}<\begin{matrix}CH_2-CH_2\\CH_2-CH_2\end{matrix}>NCH_3$$

This compound seems to differ from hetrazan in being a citrate while the earlier compound is a hydrochloride. A dosage of 6 mg. per Kg. thrice a day, for 2 to 3 weeks, is said to clear microfilaria from peripheral blood and to improve the general condition. It is claimed to be effective in *W. bancrofti, loa loa* and *Onchocercus volvulus.* Barring headache, lassitude, nausea and malaise, no serious toxic effects have been noticed. Allergic reactions occasionally noticed are presumably due to destruction of worms.

A new Sarcopticide

Eurax :—N-ethyl o-crotnotoluide, a colourless, odourless, non-staining compound in 1 per cent strength, is found to be valuable in scabies. The entire body is rubbed with this compound after a preliminary bath. A second bath is permitted after 24 hours. Several cases of scabies are being 'cured' with one such treatment. Itching disappears in about an hour of application. The eye however needs protection.

Advances in systematic Therapy

Nervous System

Procaine-intravenous :—The therapeutic uses of intravenous procaine are steadily on the increase. The hitherto unexplored actions of procaine give new promise in therapeutic usuage. Reference has been made in the earlier review in this series to its use as an analgesic in traumatic conditions. Most cases of neuritis-brachial, intercostal or sciatic, respond well. In trigeminal neuralgia, however, results are poor. Spasmodic vascular conditions are satisfactorily relieved. When hyaluronidase is added to 1 per cent procaine, analgesic action is reported to be better, due to better diffusion. Many cases of amputation have been averted.

Atropine-like and quinidine-like actions of procaine are being clarified. Some anæsthetists report favourably on the use of procaine to stop ventricular fibrillation during cyclopropane anæsthesia, though in our study ventricular fibrillation during chloroform anæsthesia was not corrected.

Tubocurarine—a recent finding :—Claude Bernard in 1857 drew the attention of scientists to the motor paralytic action of curare, but there seems to be also a central action of curare which is excitory. Tubocurarine when injected into the ventricles of the brain of cats showed increased knee jerks, improved flexor reflexes and an increase in rate and depth of respiration accompanying a rise in blood pressure. Later, general convulsions were noticed. This new action of curare on the centres, tend to modify the theory of its peripheral action. An analogy could be sought in prostigmine which augments muscle strength in myasthenia but weakens that of a normal person when given intra-arterially. Clinically the central stimulant action of tubocurarine is of no practical importance in its application for peripheral action. The local histamine-like action of tubocurarine at the site of injection has been referred to earlier.

d tubocurarine and allied curarising drugs :—Comparison between d tubocurarine, myanesin, flaxedil and decamethonium is rendered difficult. The site of action of myanesin seems to be at the synapses of the spinal cord, a true antistrychnine action.

Decamethonium established a block by a persistent end plate depolarisation analogous to an exaggeration of the normal excitant action of acetyl choline. The block by curare on the other hand is due to an antagonism to the normal activity of acetyl choline. These differences manifest themselves in many directions as in differing muscle susceptibility. Circulating adrenaline modifies the pattern of muscle susceptibility to d tubocurarine and decamethonium.

Banthine—a new anticholinergic :—Banthine bromide or B diethyl-amino ethyl xanthine carboxylate metho bromide is also called methantheline bromide. It is said to control remarkably vagotonia in peptic ulcer. The action seems to be at the post ganglionic cholinergic level (atropine-like) and also at the ganglion level (nicotine-like). The activity of the stomach is effectively controlled by the parasympatholytic mechanism. Administered in 50 to 100 mg. doses every 6 hours, day and night, hypermotility and hyperacidity of the stomach are effectively controlled. Dryness of the mouth, slight blurring of vision, gastric fullness and slight difficulty in evacuation of the bladder may be noticed (parasympatholytic effect).

Hexamethonium iodide or C 6 in 100 mg. dose also acts by impeding transmission of nerve impulses through the vagus to the stomach.

Parkinson's syndrome—therapeutic agents :—Several therapeutic agents are used in this symptom complex to combat either the depressed emotion as by synhexyl, or the rigidity of muscles by spasmolytics like parapanit, diparcol, and solanaceous alkaloids, or salivation by the parasympatholytics.

Antihistamine drugs like benadryl have also given relief. One has to be cautious in drawing conclusions about any of these drugs, or about the drug treatment of Parkinsonism in general, on too narrow a symptomatic basis. The story of parapanit is one of initial jubilation and subsequent sobered hope. Parapanit did reduce rigidity, increase mobility, modify tremors and improve speech, but all temporarily. It was thought that it primarily acted on sensory nerve endings for deep sensibility. But dizziness was more frequent here than with the belladonna alkaloids. Lysivane like diparcol is a substituted phenothiazine compound. Though belonging to the antihistamine group of drugs, it is capable of benefiting many of the symptoms of Parkinsonism, especially emotion and mentality. In doses of 200-500 mg a day, toxic manifestations were sometimes noticed such as drowsiness, cramps, dryness of the mouth, fornication, and rarely vasomotor reactions and diplopia.

CIRCULATORY SYSTEM

Rubellin—new cardiac glycoside :—Rubellin from *Urginea rubella*[13], allied to squill, is said to be 50 to 100 times as powerful as digoxin and digitoxin. Observations in man showed that the effective dose was 0.003 mg. per Kg. intravenously, acting best in auricular fibrillation and congestive heart failure. Its full action is evident in 2 hours after intravenous administration. Digitalis can however be given by mouth along with rubellin intravenously. Issacson (1950) is of the view that rubellin is bound to be a clinical competitor to digoxin. (Rubellin is not to be confused with Rubella or German measles with which it has nothing to do.)

Alcohol and Angina pectoris :—Prohibitionists were disturbed to learn that alcohol was found effective in the treatment of angina pectoris with evidence of coronary relaxation. Whisky appeared to be as effective as glyceryl trinitrite in preventing angina of effort, but a carefully controlled study by Russek (1950) revealed that whisky in 1-2 oz. failed to prevent the transient electrocardiographic alterations, *i.e.*, RS-T depression and T wave changes, observed in control records of patients with angina. In sharp contrast, 0.4 mg. of glyceryl trinitratis influenced the electrocardiographic changes showing definite coronary dilatation. Possibly the soporific effects of alcohol were responsible for clinical improvement.

Diet and Hypertension :—Since Kempner in 1945 introduced rice diet for hypertensive vascular diseases, trials have been made all over to assess the view. A ten day treatment in many cases reduced the blood pressure that kept up at 120-140 Hg. diastolic with a week or ten day rest in bed. Effects on ambulatory patients are not worth scientific scrutiny. Though the blood pressure was reduced and some symptoms relieved, the improvement was more apparent than real as gauged by the size of the heart, retinal and electrocardiographic changes.

How far is a low sodium intake (less than 200 mg. a day) responsible for this benefit? Administration of sodium chloride steadily raised the blood pressure in these cases where it had been brought down by rice diet. Sometimes rice diet reduced the blood cholesterol level. The nitrogen balance is upset in the early stages which is another factor to reckon, the balance being restored only after considerable time, say 2-4 months. The other effects are more serious. Extreme salt reduction depresses glomerular filtration and tubular reabsorption. This means impaired renal function, paving the way for future uræmia. It must be noted that in hypertensive diseases the kidney is already below par.

Renal failure is a contra-indication for sodium starvation and indirectly rice diet. In some cases the rice diet for hypertension aggravated quiescent peptic ulcer. How far low protein diet or acid juice (fruit) was responsible, it is not possible to say. However, the rice diet approach to the problem of hyperpiesia is a new venture. Its relation to sodium or chloride or both awaits clarification.

HAEMATOLOGY

Available evidence seems to favour the view that in pernicious anæmia there is a failure of absorption of vitamin B_{12} rather than destruction in the intestine or deviation to micro-organisms. The still elusive intrinsic factor appears to be vital when B_{12} is taken by mouth in physiological amounts, though ingestion of huge amounts may lead to mass action and direct absorption. It is not clear yet if the interaction with the intrinsic factor is of the nature of an enzyme reaction leading to an absorbable form of the vitamin or that the intrinsic factor is a highly specific protein, combination with which is necessary for absorption as against mere passive diffusion through the intestinal wall. But from the picture of vitamin B_{12} as it is revealed today, it rather resembles porphyrin which must be absorbed intact in a specific biological manner. The question still remains open as to whether there is not a third antianæmic factor in the liver which is different from B_{12} and folic acid. The time has therefore not yet come to discard whole liver or crude liver extract from the therapeutic armamentarium. Some, but not all cases of megaloblastic anæmia of pregnancy fail to respond to vitamin B_{12}.

Folic acid antagonists and malignancy:—Biological antagonism and allied substrate competition have provided an impetus for much pharmacological study. Folic acid antagonists, antihormones and antivitamins are being heard of much these days.

Folic acid or pteryl glutamic acid was made available at a time when it was deemed an essential factor for the growth of many organisms and for animal metabolism. It had been known to enhance the progress of leukæmias in man. Hence it was but rational that antifolic acid should reverse this process. Analogues of pterylglutamic acid may be expected to exert a biological antagonism to the parent substance.

No less than about 40 of these analogues have been prepared, of which aminopterin or 4 aminopteryl glutamic acid and amethopterin or 4 amino N 10 methyl pteryl glutamic acid and amino or 4 amino pteryl aspartic acid are studied. All these have an inhibiting effect on *L Casie* and *Str Ladis R* in media containing folic acid. When administered to animals, they induce folic acid deficiency states. Aminopterin is said to inhibit *Rous sarcoma* in chicks and a mammary tumour in mice. Amethopterin has yielded significant results in prolonging life in transmissable leukæmias in mice.

In human beings, temporary remissions are obtained in myeloblastic and monocytic leukæmias. Acute lymphatic leukæmias in children also respond favourably. Remissions however are only temporary, though the prognosis is better in children with acute lymphatic leukæmias. Monocytic leukæmias seem to be refractory. Remission is accompanied by complete return to normal of both bone marrow, peripheral blood and even joint lesions. In children 1 mg. doses daily and for adults 3 mg. doses orally could be given for a prolonged period say—3—4 weeks, provided a strict watch is kept over the blood picture and general toxic symptoms. Toxic symptoms include vomiting, diarrhoea, ulcerative stomatitis, alopecia, jaundice and in serious cases aplastic anæmia with a tendency to bleed. Whether these are symptoms of folic acid deficiency or possibly a toxic action of the antagonists is not evident.

At present their value lies in increasing the remissions for a reasonable period. Dacie (1950) [3] feels that the effect of these drugs " is to raise hopes which are dashed when the inevitable relapse occurs". We hope for better days for leukæmias with this line of treatment.

Other chemotherapeutic agents in malignancy have not been very promising either. Combination of hyperpyrexia with nitrogen mustard in Hodgkin's disease reduced the size of tumours, but neither the remission period nor other effects improved. The addition of pteropterin or diopterin did not materially add to the benefit.

Chymotrypsin, a protein enzyme gave immediate relief from pain in some cases of malignant neoplasms and reduction in size. A wider trial did not answer satisfactorily. Autopsy did not reveal any degenerative changes in the malignant growth.

A new Anticoagulant :—Phenylindone dione, a new synthetic anticoagulant in doses of 25 to 100 mg. per Kg. orally or intravenously, effectively delayed clotting in coronary thrombosis. In thrombophlebitis or coronary thrombosis, the prothrombin level fell to 25-30 percent of normal in a few hours and remained so for about 24—48 hours. A maintenance dose of 50 mg. per Kg. per day may be necessary to keep the prothrombin level at 30-40 percent of normal. Overdosage may lead to spontaneous bleeding. A mild fatty degeneration may be noticed, which disappears on stoppage of the drug. It is weaker than dicoumarol.

HORMONES

Antihormones :—Distressing data are forthcoming to indicate the reason for refractoriness in some cases of hormone therapy. Repeated injections of thyrotropic or pituitary or chorionic gonadotropic hormones into animals of different species induce a refractory state in which the animals become resistant to further effects of the hormones. Antihormones are actually demonstrated in the sera of these refractory cases. This refractoriness can be passively transmitted to other animals. The hormones seem to behave as antigens while the antihormone has many of the properties of an antibody. There is some evidence that A C TH can also provoke an antibody as revealed from the works of Gordon (1950) [5].

The significance of these animal experiments in relation to man is not yet clear. No work has been done to reveal anti A C T H in patients treated for a prolonged period with this hormone though there is a suggestion from experimental observations. Resistance to treatment or decreased response to treatment may well be anticipated and this is a prospect too gloomy to contemplate.

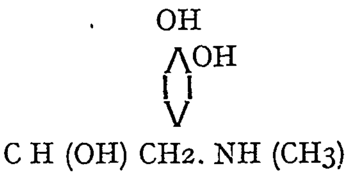
Similar is the possibility with vitamins, that anti-vitamins are capable of being formed in the body.

A new Antithyroid :—Mercaptoimidazole in 60 mg. doses was found to be effective in many cases of thyrotoxicosis. The superiority of this compound over the thiouracil series lies in its reduced toxicity. Neurotoxic manifestations of thiouracil, methyl, propyl, cyclopropyl thiouracils were due to depression of the peroxidase enzyme system not merely in the thyroid where it is desired, but also elsewhere in the nervous system where it is not desired. Increased activity and reduced toxicity of 2 mercaptoimidazole makes it a valuable therapeutic agent.

Adrenaline—changing concepts of its action :—The sympathetic nervous system, with regard to adrenaline and "nor-adrenaline, is proving exciting, revolutionary and annoying. Stimulation of the sympathetic nerves necessitated the assumption that two different active substances,(*i.e.*, sympathin E and sympathin I ,with excitatory and inhibitory effects) were produced. These substances were thought to be formed by the interaction and mediation between constituents of the reacting cells. It was thought that nor-adrenaline might be responsible for the excitatory action and adrenaline for the inhibitory action. The difficulty for the pharmacologist today is to assess the relative action of the new 'nor-adrenaline' and its time honoured homologue 'adrenaline'. In structure, nor adrenaline is similar to adrenaline except that the nitrogen of the amine group in the side chain is not methylated. Prof. Von Euler of Copenhagen (1951) [15] noticed that nor-adrenaline is the physiological transmitter of adrenergic action and when the nerve is cut and allowed to degenerate, nor-adrenaline almost disappeared from the organs supplied. And yet, the sympathetic transmitter is not entirely nor-adrenaline ; adrenaline also had a hand. This relationship awaits elucidation.

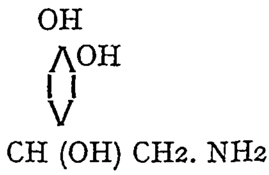
In tumours of the adrenal medulla there is found an excess of adrenaline in the blood which is excreted in urine in a potent form.

Nor-adrenaline did not affect oxygen consumption of the tissues while adrenaline did, significantly. Nor-adrenaline produced a rise in systolic and diastolic pressure and bradycardia, while adrenaline caused only a systolic rise and often a fall in the diastolic. The sum total of the adrenaline effect seems to be a vasodilatation while nor-adrenaline gives evidence of a general vasoconstriction. Nor-adrenaline is therefore linked with hypertension, an error, as it is thought, in deficient transmethylation for conversion into adrenaline.



$C\,H\,(OH)\,CH_2.\,NH\,(CH_3)$

Adrenaline



$CH\,(OH)\,CH_2.\,NH_2$

Nor-adrenaline.

It looks as though nor-adrenaline is the main sympathetic neurohormone for general service, adrenaline acting as a mere adjunct for special purposes with reference to metabolic processes. Nor-adrenaline is not merely a precursor of adrenaline, for there is evidence of normal reflex vascular effects being mediated mainly by nor-adrenaline. That hypertension is possibly due to imbalance between the two types of sympathetic transmitter is a surmise from these data but nothing of immediate therapeutic significance has emerged so far. Many more gaps need filling for a clearer knowledge of the role of these two substances in sympathetic action. A wide field for exploration exists here.

Adrenaline substitutes :—Orthoxine is a synthetic sympathomimetic having a high bronchodilator effect with minimum pressor effects, or unpleasant effects on the C.N.S. Isuprel is an isopropyl modification of adrenaline. It is a potent bronchodilator but without the blood pressure raising properties. It however augments the heart rate.

Insulin and Cortisone :—A preliminary report suggests that insulin has a cortisone sparing action and that economy may be effected by administering the two together. Cortisone possibly effects a synthesis of a tissue carbohydrate and in this insulin is helpful in sparing and preventing the conversion of amino-acids. If with 50 mg. of cortisone 40 units of insulin are added and administered for a week or ten days, the clinical condition improves as though 100 mg. of cortisone alone were administered daily, for the same period. Hypoglycæmia was readily controlled and was not related to the degree of response.

Further studies are being made to reduce the amount of cortisone needed therapeutically by other hormonal combinations.

Diethylstilbœsterol in orchitis of mumps :—Diethylstilbœsterol has been found effective in reducing the morbidity in testicular complications of mumps.

ANTIHISTAMINICS

The study of the action of antihistaminics has revealed strange properties. Apart from the anti-allergic or antihistamine properties, these compounds seem to show anti-adrenaline and anti-acetylcholine actions. We are so accustomed to look upon adrenaline and acetyl choline or histamine and adrenaline as antagonists, that we cannot conceive their being related substances linked to one another in their actions.

Again, an antihistamine property could be obtained from anti-acetylcholine or adrenaline-like compounds, as in asthma, which could be relieved by atropine, adrenaline or antihistaminic.

It was shown long ago that in denervated skeletal muscle, the action of acetylcholine could be either potentiated or inhibited by adrenaline. It looks as though acetylcholine synthesis is the basis of normal function of all tissues, be it heart, intestine, vessels, bronchi, or the C.N.S., and that the effect of acetylcholine so produced is either potentiated or inhibited as necessary by adrenaline or histamine or its synthesis and liberation being determined by all. Strong evidence has been brought forward by Burn (1951) [2] that contractions of the auricular muscle are proportional to the amount of acetylcholine synthesis. The existence of two actions of acetylcholine on cardiac muscle is being proved; the contrast between the stimulant action on skeletal muscles and inhibitory action on cardiac muscle is no longer tenable or complete. Acetylcholine synthesis in the heart may be responsible for exciting the contraction in the same way as it excited contraction of the skeletal muscles when liberated by a motor nerve.

These are the data to show that the attack of the three mechanisms, *i.e.*, histamine, acetylcholine or adrenaline can produce the same result depending on the condition of the organ. We can thus conceive how an anti-allergic drug which affects one of them in some degree inhibits the other two and how such a drug may have many properties. They may prolong the refractory period of the heart muscle (quinidine-like), neutralise the histamine action in the nasal mucous membrane and skin, (antihistamine) exert a depressant action on the vestibular apparatus of the C.N.S. or reduce gastric secretion (anti-acetylcholine).

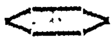
Thus we are led to the concept that histamine, adrenaline and acetylcholine act as local hormones and govern tissue activity in most organs. Again, local anæsthetics like procaine, analgesics like pethidine, sympathomimetics like ephedrine have antihistamine actions. Antihistamines are therefore expected to show several side effects which may in themselves be useful.

Local anæsthetics like procaine and amethocaine, have quinidine-like actions, as also spasmolytics like atropine, papaverine, trasentin and pethidine. Anthisan is twice as active as quinidine and also has analgesic properties. Benadryl, like atropine causes drying of the mouth and like pethidine causes mental confusion. Most antihistaminics are useful in sea sickness, like hyoscine, though the value of hyoscine is doubted by many.

Atropine-like antihistaminics can abort a common cold by drying up secretions. Benadryl was found useful in myotonia, like quinine.

The basis of these common properties is that these substances depress either acetylcholine or histamine or adrenaline action in different tissues.

Dramamine, a combination of benadryl with theophylline to which a chlorine atom is added, is popular in America as a remedy for sea sickness. It neutralises D F P which has an acetylcholine prolonging action. Dramamine alone among the antihistaminics is said to cause vasodilatation while other antihistaminics have mainly a vasoconstrictor action. Dramamine was found to control pregnancy vomiting in 100 mg. doses three times a day as also irradiation sickness and vomiting due to vestibular damage. The use of antihistaminics in acute nephritis is not very encouraging though some have reported good results in nephritis following scarlet fever.

Toxic action :—A few cases of damage to the blood forming organs after antihistaminics like pyribenzamine and diatrin when given in 50 mg. doses thrice a day are reported. But the granulocytopænia was not serious, as stoppage of the drug and administration of penicillin or blood transfusion reversed the process. Possibly this effect is due to a benzamine linkage  —N< for amidopyrine with a similar linkage also causes agranulocytosis while benadryl which has no such linkage has not produced agranulocytosis. This is a danger sign post against the indiscriminate and prolonged administration, or worse, self medication of antihistaminics for all and sundry ailments.

FLUORIDES

Fluorine in drinking water is said to have reduced dental carries during the past 6 years by 60 percent according to the American water works association. In the next ten years, most U.S.A. cities would be adding fluorides to their drinking water. It is thought that fluorination of drinking water is "the biggest step in public health in the last 100 years".

CONCLUSION

One is drawn to strange conclusions from the hopeful outlook engendered by progress in therapeutics. The war against diseases looks practically over; man is liberated. But for what? For a longer span of life? Hordes of people who would otherwise be dead are saved by the therapeutics of today. The aged who are kept alive are not merely to vegetate but to be productive. As Harry Beckman observes in his preface to the year book of therapeutics 1951 "......we are obtuse indeed if we expect gratitude from the youthful majority when this act will engulf in economic desperation.....unless we devise newer walks of life for the old to work....else children will fling their parents to the state". To be old is a prospect too gloomy to contemplate. We should convince political leaders that without ensuring the productive existence of the aged (by aged one means men over 55 when most government think men are superannuated) their vaunted existence is a mere shibboleth.

Health they say is wealth but is it 'health thus far and no further'?

REFERENCES

1. Beckman H.: Year Book, Year Book Publishers, Chicago, 1949.
   (Most references are from this).
2. Burn, J. H.: Pharmacological Action of Antihistaminics B.M.J. **2**: 691:693, 1950.
3. Dacie, J. V.: Folic Acid Antagonists in Acute Leukæmia B.M.J. **1**: 1475-1476, 1950.
4. Garrod, L. P.: Reaction of Bacteria to Chemotherapeutic Agents B.M.J. **1** 210, 1951.
5. Gordon, J. S.: Antihormones and ACTH B.M.J. **2**: 156, 1950.
6. Hench, P.: The Adaptation Syndrome B.M.J. **2**: 941-943, 1950.
7. Issacson: S. African Med. J. **24**: 901, 1950.

8. Iswariah, V.: Progress in Therapeutics. I.J.M.S. **4** : 200-225, 1950.
9. Jeffries, F. J. G. : Treatment of Early Syphilis with Penicillin Neoarsphenamine and Bismuth and with Penicillin and Bismuth Alone. Lancet **1** : 83-85, 1951.
10. Kersley, G. D. *et al.* : Insulin and Electroconvulsive Therapy and Rheumatoid Arthritis B.M.J. **2** : 855-860, 1950.
11. Med. Res Council of Britain : Chemotherapy of Tuberculosis B.M.J. **2** : 1102-1103, 1950.
12. Mayo Clinic Report : Quoted in B.M.J. : Cortisone and ACTH B.M.J. **2** : 1375, 1950.
13. Russeck H. I *et al.* : Alcohol in the Treatment of Angina Pectoris J.A.M.A. **143** : 355-357, 1950.
14. Spies T. D. *et al.* : Response to Adrenocorticotrophic Hormone and Cortisone Lancet **2** : 241-244, 1950.
15. Von Euler : Adrenaline—Newer Concept B.M.J. **1** : 105, 1951.
16. W. H. O. Experts Committee on Malaria : Ani-malarial Drugs Lancet **2** : 297, 1950.

GENERAL THEORY OF BACTERIOSTASIS AND ITS APPLICATION TO SULPHA DRUGS

To the memory of Paul Ehrlich (1854-1915)

M. G. Good *

DEFINITION

Bacteriostasis means the inhibition of growth of micro-organisms by certain drugs. Bacteriocide or disinfection designates the death of germs by similar or allied methods. It is probably correct to say that bacteriostasis and disinfection are fundamentally the same phenomenon, differing only in quantity or grade as far as the antimicrobial effect is concerned.

MORPHOLOGY AND MICROCHEMISTRY OF THE BACTERIAL CELL

In order to know what parts of the bacterial cell play a role in bacteriostatic and bacteriocidal processes, it appears pertinent to discuss very briefly the morphological and cytochemical structure of bacteria and their difference from animal cells. All the observations and facts in biology and medicine show conclusively that the animal or plant cell, during its life, is capable of maintaining its "milieu interieur" (Claude Bernard), inspite of differing and sometimes adverse conditions of its surroundings, at least to a very great extent. Physiologists have therefore rightly postulated that a living unit—the cell—possesses an outer physical line or border allowing it to accept from the surrounding medium in a very *selective* way those substances required for the continuation of life, but refusing entry into the cell, other harmful substances. What is still in dispute is, whether the external layer, called membrane in animal cells and ectoplasm in bacteria, is a functional or anatomical structure making an individual life of its own possible or not.

More than twenty years ago new staining methods were developed by the writer which demonstrated the presence in every bacterium and yeast cell of an anatomical membrane as well as a well defined nucleus (macrogranulum), stained in contrasting colours. By means of similar staining methods animal cells (liver, kidney, muscle, etc.) too, could be shown to possess a distinct membrane beyond the shadow of doubt.[2]

CHEMISTRY OF BACTERIAL ECTOPLASM AND CELL MEMBRANE

Biochemistry has rendered innumerable services to biology and medicine by isolating and synthesizing many substances present in and

---

* London, N. W. 11.

produced by living cells. But what organic chemistry by its very nature cannot decide is, in what morphological parts or elements of a cell or tissue, are these chemical substances contained. In this connection the work of the botanist Hansteen Cranner[1] must be mentioned who isolated from potatoes and peas, the so called "water soluble phosphatides". These proved to be complicated organic compounds (Græfe and Magistris)[4] consisting of a diamino-phosphatide bound to a polyose and anthocyanine radicals which give a precipitate with basic dyes. For the study of micro-(cyto)-chemistry the dermatologist P. G. Unna[9] introduced "chromolysis" which consists in staining selectively special structures or elements—*e.g.*, nucleus, granules, etc., of cells or tissues by specific staining methods and determining by what solvents, if any, they can be removed, so that the same staining methods when applied after that treatment give a negative result. By means of chromolysis it could be shown that yeast and bacteria, contain in the ectoplasm a phosphatide which is bound to a basic substance, possibly a polysaccharide. The phosphatide could be removed from the ectoplasm by HCI-alcohol. Macroscopically, such water-soluble phosphatide could be isolated from yeast. It is noteworthy that this phosphatide of the ectoplasm-ectolipid—differs in quality between gram-positive and gram-negative bacteria and is responsible for the positive Gram stain of the former.[2]

ANATOMY OF DISINFECTION

What anatomical parts of the bacterial cell are affected by disinfection? The problem was studied by means of solutions of suitable metallic salts and dyes, to which yeast and bacteria were subjected. In the case of Fe_2Cl_6, $AgNO_3$ and $HgNO_3$ it was shown by specific chemical reactions, microscopically, that the metal was deposited in the membrane or ectoplasm of the yeast and micro-organism treated; in the case of other metallic salts the same microscopic result was arrived at, *e.g.*, with $ZnCl_2$, Pb-acetate, $AlCl_3$ and Bi-mannose by means of hæmatoxylin, an acid organic dye, which in watery solution does not stain but gives beautifully coloured stained reactions after mordanting with the above mentioned metallic cations. The ectoplasm especially of yeast cells often showed a double-contoured membrane. Morphologically identical microscopic results were found with basic dyes like Victoria blue, fuchsine, saffranine and methyl violet added in solution to a suspension of living yeast and other micro-organisms. It is obvious that in this case "vital staining" is nothing else but a bactericidal process since the dyes concerned are more or less toxic to bacteria, often in high dilutions. On the basis of these findings and a full review of the literature on disinfection the following conclusions regarding the bactericidal effect of metallic salts and basic dyes were arrived at:—

(1) The effect was due to their affinity to the phosphatides-phospholipins, present in the bacterial cell membrane where the respective cations are deposited.

(2) The affinity of these cationic disinfectants to the membrane is of a chemical nature or "electropolar absorption".

(3) The process is a reversible one, *i.e.*, under certain conditions it could be reversed and the apparently dead bacteria revived.

(4) The bacteriostatic and bacteriocidal effect of basic dyes on yeast and bacteria depends to a large extent on their

$$\text{biological partition coefficient} = \frac{\text{solubility in membrane lip.}}{\text{solubility in solvent.}}$$

This factor corresponds, to that, which according to Meyer-Overton's Law, plays a decisive role in narcosis, or general anæsthesia.

THEORY OF VITAL STAINING

There are many dyes on the market, especially the basic ones which are known to be toxic to micro-organisms. It was, therefore, evident that a thorough study of the factors governing vital staining might help to elucidate the mechanism of bacteriostatic and bacteriocidal effects. A macroscopic method for the study of the problem was developed; a 20 percent suspension of fresh baker's yeast was shaken with a 1 percent solution of basic or acid dyes and after sedimentation the colour of the sediment and supernatant fluid was compared. On the basis of a great number of synthetic dyes of different chemical structure being investigated, the following conclusions were arrived at:—

(1) The permeation of *basic* dyes depends on (*a*) the biological partition coefficient, (*b*) their reducibility by living yeast and bacteria and (*c*) the amount of precipitation of the individual dye by Cranner's phosphatide.

(2) Acid synthetic dyes, especially if lipoid soluble, (*e.g.*, eosine) are easily and highly colloidal, (*e.g.*, trypan blue), and relatively copiously taken up by yeast cells. In contrast to current opinion, non lipoid soluble acid dyes, (*e.g.*, water blue) permeate also but to a smaller extent.

(3) Living animal cells, *e.g.*, from thymus behave in general, like yeast, when subjected to the same experimental conditions.

(4) Living protozoa like paramæcia are also permeated by non-lipoid soluble acid dyes.

The permeability of soluble non-lipoids and easily water-soluble dyes, seemed to be in striking contradiction to the lipoid theory of vital staining. But the difficulty was overcome by the hypothesis that acid dyes permeate the lipoid membranes of plant and animal cells in the form of their free acids and the conception of the pH gradient. The free acids are usually well soluble in organic solvents, but extremely little in water and permeate under conditions of a different pH within and outside the cell. A positive gradient, *viz.*, a change of pH from alkaline (outside) to less alkaline (inside) favours the penetration of basic dyes (free base) and inhibits that of acid dyes. A negative pH gradient, *viz.*, change of the pH in the opposite direction from acid to less acid favours the permeating of acid and slows down that of basic dyes into the living cell [2].

Generally speaking, the well known fact that basic dyes are more toxic to bacteria as compared with acid dyes was accounted for by the following fundamental difference: the former are distinguished by a greater and more intimate affinity to the lipins of the cells which are of a chemical, or what amounts to the same, of an electropolar nature, whereas the latter are taken up by means of solution, hence by physical affinity only. The fundamental difference is evidenced by the finding that the toxicity of metallic salts for micro-organisms, which was known to decrease in the series, Hg Ag Zn Cu, is paralleled by the series, Hg Ag Zn Cu Ba Ca which was found to correspond to the precipitability by a water soluble phosphatide. Acid dyes are not precipitated by that phosphatide, but basic dyes are precipitated and apparently corresponding to their toxicity to micro-organisms.

ACCUMULATION OF DYES IN GROWING BACTERIA [2]

When yeast and bacteria are grown on solid media, containing acid dyes, or basic dyes in great dilutions, the cultures are beautifully coloured and often show an accumulation of the dye, *e.g.*, Congo red within the cell in the form of amorphous granules. It was found that in general an acid pH of the medium favours the penetration of acid and a slightly alkaline pH, that of the basic dyes. In order to test the hypothesis of the pH gradient it appeared necessary to determine the intracellular pH of yeast and bacteria.

INTRACELLULAR pH OF BACTERIA

A simple technique of adding different indicators to the nutrient medium and the bacteria streaked on the solidified plates was used. Among a great number of indicators tried, the following four proved of decisive value for the determination of the intracellular pH: cresol purple, phenol red, bromethymol blue and cresol red. Bacteriologists classify micro-organisms under two headings; gram-positive bacteria, taking the Gram stain and gram-negative bacteria taking the counterstain (fuchsin) in the identical procedure. The experiments led to remarkable results, that, with a few exceptions, the former have a slightly acid pH ranging from 6.1 (yeast) to about 6.4—6.6. On the other hand the gram-negative organisms showed in the majority, a pH of 7.4—7.6. Among the latter the only exceptions were *Neisseria gonorrhoea* and *Neisseria catarrhalis*, with a very slightly acid pH, contrasting with the meningococcus and the *vibrio choleræ* with pH 7.0—7.1.

A few observations of a general interest may be specially mentioned. The intracellular pH of micro-organisms is not an absolute constant, but depends to a slight degree on the pH of the medium, *viz.*, slightly more acid when grown on a medium of pH 6.5 than on normal plate which has a pH of 7.8. Secondly, it varies with the age of the culture, becoming more alkaline after 3-4 days. Only the paratyphoid, Gaertner's and Hay bacilli became more acid with advancing age. Thirdly, in examining a great number of coli and paratyphoid strains kept in our laboratory a very remarkable phenomenon was observed that some of the strains showed a slightly acid pH in contrast to the majority with an alkaline pH.

BACTERIOSTATIC EFFECT AND GRAM STAIN

The Gram stain was firstly only of diagnostic and tinctorial interest but proved later on to have an important bearing on the question of bacteriostasis. It was demonstrated (Churchman, 1913, Fisenberg, 1914) that many basic dyes—the toxophoric cation group—inhibit the growth of gram-positive bacteria in high dilutions, in striking contrast to their opposite numbers. On the other hand some acid dyes-toxophoric anion—and the salts of chromic acid showed just a reversed effect; *viz.*, greater toxicity to gram-negative organisms as compared with gram-positives. This extremely strange phenomenon which appeared very difficult to explain was accounted for by the writer as due to their different intracellular pH.

Diagram

gram + ve cell				gram — ve cell
pH=	+ gradient	medium	—gradient	pH=
6.4		pH 7.2		7.4—7.6

Bacteriostatic and bacteriocidal investigations are usually conducted by growing the micro-organisms on an approximately neutral medium-pH 7.2. As can be seen from the diagram, a basic dye, when added to the medium permeates the gram-positive cell easily, because of the positive pH gradient, but much less a gram negative cell with a negative pH gradient. In the case of an acid dye or a chromate compound being of the toxophoric anion group—the reverse mechanism is prevalent. This disinfectory effect is in agreement with the lipoid Theory of Vital Staining. Let DbCI represent a basic dye—Db the tinctorial cation. If the solvent or medium is alkaline it will contain DbOH, which being a free base is well soluble in alcohol, but sparsely soluble in water, will easily penetrate the bacterial membrane. Provided the intracellular pH is acid, as in a gram-negative microbe, it will be transformed into the soluble salt. In this way the cell will selectively take up the dye in a higher concentration than the solvent. But if the intracellular pH is alkaline or more alkaline than the medium every molecule of DbCI after permeation of the membrane will become DbOH and leave the cell, passing into the medium. A reverse mechanism can be predicted for an acid dye—DaNa, where Da is the tinctorial anion—will accumulate in a gram-negative cell (slightly alkaline intracellular pH), but return to an alkaline medium from a cell with an acid or less alkaline intracellular pH. This is the result of a dynamic process, *viz.*, the balance between the number of molecules of the dye entering from the medium and those leaving the cell into the medium by permeation of the membrane in the opposite direction.

It is a generally well known fact that acid dyes and acid compounds are as a rule less toxic to microbes and animal cells; it is accounted for by the conception that they are present in the cell constituents in the form of a solution or physical fixation, in contrast to basic substances which are very likely fixated to membrane lipins by chemical affinities or at least by electropolar adsorption. The observation that bacteria are negatively charged as evidenced by cataphoresis, lends I think, good support to the contention of a fundamental difference between basic and acid substances for the life of microbes (and animal cells too).

ATREPTIC THEORY AS A GENERAL MECHANISM OF BACTERIOSTASIS AND DISINFECTION (BACTERIOCIDE)

The writer has shown that Cranner's watersoluble phosphatide (from peas and yeast) possesses the property of an enzyme, *viz.*, oxidase: it is capable of synthesizing β-naphthol + phenylenediamin to indophenolblue (Nadi-reaction). At the same time the phosphatide reduces dyes like methylene blue and $KMnO_4$. It is worthy of note that the capacity of the phosphatide for oxido-reduction was found to amount numerically to 20 times, the same (moist) weight of living yeast. The phospho-lipin was precipitated by basic dyes, the dilution of which varied with the individual dye, but not by acid dyes. I think that it can, without fear of contradiction, be maintained that a bacteriostatic agent or disinfectant after having penetrated into the outer layer or envelope of a microbe must interfere with its metabolism to a larger or smaller extent. It would appear likely that the "life" of a cell-plant or animal—consists in a continuous alternating process of oxidation and reduction, following each other with more or less regularity, which supplies the living unit with the required energy. The impaired metabolism of a microbe as a result of drugs or foreign compounds entering its outer layer can reasonably be explained in general physiological terms as due to its isolation from the nutrient medium which of necessity leads to starvation. No doubt the most elemental "food" indispensable for the continuation of life is oxygen as can be seen from the fact that animals and humans can live without food for weeks, without water for days, but without oxygen only for minutes. I, therefore, feel justified to postulate that the Atreptic Theory gives the most general mechanism of the bacteriostatic and bacteriocidal action of inorganic and organic compounds. The theory seems to account for many more factual observations regarding the biology of microbes, which, however, cannot be gone into, owing to lack of space. But I wish to mention only one point. Why is it possible to kill pathogenic bacteria lavishing in the blood and tissues of a living animal by an appropriate chemotherapeutic agent, without materially damaging the hosts? The probable reason appears to be the fact that the "specific surface", *i.e.*, surface volume coefficient or the surface compared with the volume and mass in micro-organisms is relatively very high. A bacteriologist has published the following interesting computation. A cube of 1 cm. diameter can be divided into lo ^{12} cubes of 1μ side, each of which can easily accommodate a coccus of 1μ diameter. This cube of cocci weighs 1.25 gram, has a volume of 0.523^3 cm. ($= \text{lo}^{12} \times 0.523^3$) and an "inner surface" of not less than 3.14 square metres ($= \text{lo}^{12}.\ 3.14^2$). In passing, I mention here that very recently (1949) E. A. Hauser *et al*[5] have proved by direct ultra-violet microscopy that penicillin, an acid antibiotic, is absorbed on the surface of *staphylococcus aureus*.

DEDUCTION FROM THE ATREPTIC THEORY

In trying to account for the effects of a bacteriostatic, microbiologists, almost without exception, think in the first place of its action on the proteins of the germs which are said to be precipitated or denaturalized by the pharmacon. The new theory, however, makes it appear worthwhile to consider the question of phospholipins versus proteins as the basis of the process. According to the atreptic theory phosphatides and probably other lipids contained in the superficial layer, the ectoplasm of the micro-organisms, are the main chemical substances acted upon in bacteriostasis and its highest degree, disinfection. If the theory can be proved to be true, it will amount to a dethronement of proteins, as playing everywhere the most important and exclusive role in the life of microbes under normal and pathological conditions.

In pursuance of his celebrated "side-chain theory" Ehrlich, the founder of modern chemotherapy, postulated that the efficacy of a chemotherapeutic agent is due to specific "chemoceptors", (*e.g.*, acetylchemoceptor in arsacetin) which are responsible for its greater affinity to a specific germ as compared with the host cells and tissues. In the light of the present advanced knowledge Ehrlich's ingenuous conception appears no longer tenable. The changes brought about in a chemotherapeutic agent by alteration of its side-chains (chemoceptors) is according to the atreptic theory caused by the fact that the former alter the partition coefficient and/or the basicity/acidity of the compound concerned, which leads to an increased or diminished affinity to the pathogenic germs as compared with the host cells, especially the most sensitive organs, central nervous system and other vital organs, of the host. In other words the side-chains alter the distribution of the chemotherapeutic between bacterial and host cells, *i.e.*, bacteriotropy and organotropy in Ehrlich's picturesque terminology. The object of experimental pharmacology is, according to Ehrlich, to find or construct a compound X which has a greater affinity to a specific germ than the host cells, *viz.*:—

bacteriotropy X organotropy.

In the light of the atreptic theory this object can be more clearly defined by the formulation :

bacteriolipotropy X organolipotropy.

APPLICATION TO SULPHONAMIDES

Generally speaking the sulpha drugs are bacteriostatic against gram-positive bacteria (with a few exceptions). Bacteriologists and physicians have been baffled by the strange fact that the efficacy of the sulphanilamides should depend on a tinctorial criterion, *i.e.*, the Gram stain of the pathogenic organisms. But it is in full agreement with the theory, that compounds are basic substances and owing to the alkaline reaction of the blood a positive pH gradient exists towards gram-positive bacteria (acid intracellular pH) which favours their permeation into the germs. It is worth stressing that the theory, especially as far as the pH gradient is concerned, only postulates that in case of gram-negative bacteria with an intracellular pH of 7.4—7.6 a basic chemotherapeutic does not act as favourably. Under favourable conditions, *e.g.*, higher alkaline PH of the medium the sulpha drugs act on gram-negative microbes also. This is in keeping with clinical observations ; in intestinal infections (alkaline pH) they are effective against gram-negative pathogens, e.g., dysentery, asiatic cholera, especially compounds like sulphaguanidine, sulphasuxidine which are slowly absorbed into the blood and therefore make possible a prolonged effect on the microbes of the intestines. In a similar way sulpha drugs are bacteriostatic against almost all urinary infections, especially when the urine is kept at a slightly alkaline reaction. Against the gram-negative *Escherichia coli* they have been proved to be much more effective at pH 7.7 than at 6.2—7.0. Since

90 per cent of the drug is excreted into the urine, the sulphonamides are here even bacteriocidal (Goodman & Gillman, 1942),[3] proving my contention that there is no fundamental difference between bacteriostasis and bacteriocide, the latter being obtained at a higher concentration of the drug. As an illustration of the importance of the pH for bacteriostasis I mention the following observations: sulpha drugs are effective against the gram-negative meningococcus from the blood, but not by intrathecal injection (pH slightly acid), not effective against established abscesses, evidently because of the acid pH. By contrast, mandelic acid and also benzoic acid are bacteriostatic in urinary infections only in acid urine. Sulphanilamides are effective against the gonococcus which exceptionally has an almost neutral intracellular pH of 6.8—7.0. They are poorly absorbed from the stomach (acid reaction) but readily from the intestine (alkaline pH).

The role of the physical properties of solubilities and the partition coefficient of a drug in bacteriostasis is evident from the fact that "all sulphanilamides are sparingly soluble in water". In this connection the following observation is worth quoting here: "no ready explanation is available to account for the fact that certain non-ionized organic mercury-containing compounds are far more toxic to bacteria than the highly ionized $HgCl_2$" (Goodman & Gilman, p. 826).[3] The observation is well in keeping with the Atreptic Theory, that the greater bacteriostatic efficacy is due to the diminished solubility in water. The same phenomenon has been known in regard to phenols. Na-phenolate is ineffective as a disinfectant, in striking contrast to phenol, which is well soluble in organic solvents, but less so in water. But a solution of phenol in oil is ineffective (R. Koch, 1886).

PHENOMENON OF RESISTANCE AND DRUG-FASTNESS

Since the beginning of experimental chemotherapy, clinicians and microbiologists have been baffled by the phenomenon of resistance of some microbial germs of a species normally sensitive to a chemotherapeutic agent. With regard to sulphonamides it was found soon after their introduction into medicine that susceptibility varies greatly in different bacterial species, in cultures as well as in disease. Apart from this spontaneous resistance, an acquired one or drug-fastness is met with. The acquired resistance, if present, is usually to most sulpha drugs, but not to penicillin (acid compound). It develops gradually in some degree, never completely, on continued exposure of cultures *in vitro* to sulphonamides, or in disease when unsuccessfully treated with insufficient doses. No explanation has been forthcoming to account for this strange phenomenon of drug-fastness. The writer therefore would like to suggest an explanatory hypothesis.

DRUG-FASTNESS AND ALTERATION OF INTRACELLULAR pH.

It was mentioned above that the intracellular pH of bacteria is by no means a constant, but may vary with the age of the microbes. It was further established that among a large number of strains of *Escherichia coli* a few showed a different, more acid pH, in striking contrast to the majority of the strains. The observations make the hypothesis appear reasonable that drug resistance, whether spontaneous or acquired, may be due to a change of the intracellular pH of an individual bacterial strain. Acquired drug-fastness could possibly be brought about by "breeding-out", *i.e.*, by slowly weeding out of the susceptible individual germs and propagation of the individuals with a more favourable intracellular pH. The hypothesis can easily be tested by a simple laboratory technique of pH determination. Unfortunately the writer has up to the present not been able to obtain such facilities in London research institutes.

MECHANISM OF SULPHONAMIDE ACTION

Henry (1944) [6] has dedicated an extensive treatise to the subject. On the basis of the generally confirmed observation that para-aminobenzoic acid (PABA) counteracts the bacteriostatic effects of sulphonamides, Woods and Fildes (1940) advanced the theory that sulpha drugs compete with the chemically related PABA which is an essential metabolite required for microbial growth. However PABA is not required by most pathogenic bacteria. Based on a very thorough and exhaustive study of the literature Henry concludes, "there seems to be much reason for grouping the sulphonamides with such so-called indifferent inhibitors." Sevag and co-workers (1942) [7] have established that oxygen consumption in bacteria is in fact inhibited by concentrations of sulphonamides which stop growth. The action of sulpha-drug antagonists like PABA is then simply explained by their excluding the chemotherapeutic from the cell. It would thus appear that this mechanism is in full agreement with the Atreptic Theory propounded in this paper.

SUMMARY

1. Bacteria possess an *anatomical* outer layer, ectoplasm, as proved by special staining methods. By means of "chromolysis" and other methods it was established that bacterial ectoplasm contains a water-soluble (Cranner's) phosphatide, probably bound to a basic ground substance.

2. By microchemical and microscopical methods respectively, it was found that in disinfection, the cation of metallic salts and basic dyes (vital staining) are deposited in the bacterial ectoplasm, the outer

layer of the organism.

3. The bacteriostatic and/or bacteriocidal action of these toxic basic compounds depends on (*a*) the partition coefficient, and (*b*) their affinity for the phospholipins of the bacterial membrane, which is of a chemical nature, or at least due to "electropolar adsorption".

4. Acid substances with bacteriostatic properties act, with a few exceptions, by their physical affinities for the germ only. Acid dyes are not precipitated by water-soluble phosphatides.

5. The toxicity of metallic salts decreasing in the series Hg Ag Zn Cu is paralleled by their precipitability by a water-soluble phosphate from yeast, which diminishes in the series Hg Ag Zn Cu Ba Ca.

6. The permeation of basic and acid dyes into bacterial and animal cells depends, apart from their biological partition coefficient, materially on the pH gradient, *i.e.*, the difference between the intracellular pH of the cell to be permeated and the pH of the vehicle.

7. Gram-positive bacteria have a slightly acid pH of 6.1—6.4; gram-negative bacteria have a slightly alkaline pH.

8. The different susceptibility of gram-positive and gram-negative microbes to disinfectants and chemotherapeutic agents can reasonably be explained by their different intracellular pH.

9. Atreptic Theory of Bacteriostasis: the mechanism of bacteriostasis and disinfection can be formulated in general pharmacological terms as an effect due to the penetration of the agents into the outer bacterial layer—the ectoplasm—, which leads to the isolation of the microbes from the nutrient medium, hence to starvation and especially to deprivation of the most basic supply of oxygen.

10. The experimental and clinical data on sulphonamides appear to be in full harmony with the postulates of the Atreptic Theory.

REFERENCES

1. Cranner, B. H.: Untersuchungen ueber die Frage, ob in der Zellwand loesliche Phosphatide vorkommen. Planta, vol. 55.

2. Good, M. G.: Urber die færberische Darstellung des Bakterienektoplasmas. Zugleich ein Beitrag zur Theorie der Gramschen Færbung. Cbl. Bakt. Orig. **93**: 235-237, 1924.

   Das Ektoplasma der Bakterien I. Ueber eine allgemeine Methode zur Darstellung des Ektoplasmas der grampositiven Bakterien ibid. **94**: 393-402, 1924.

   Das Ektoplasma der Bakterien II. Ueber færbrische Verschiedenheiten zwischen grampositiven und gramnegativen Bakterien. Ein Beitrag zur Theorie der Gramschen Færbung. ibid **94**: 145-150, 1925.

   Das Ektoplasma der Bakterien III-IV. Morpholgie und Aufbau des Ektoplasmas der grampositiven Bakterien. ibid. **95**: 1-20 1925.

   Ueber den Kern und den allgemeinen Bau der Bakterien. Sugleich ein Beitrag zue Theorie der Lipoidfærbungen ibid. **95**: 357-388 1925.

Das Ektoplasma der Bakterien V. Færberischer Nachweis und chemischer Bau des Ektoplasmas der gramnegativen Bakterien ibid. **100** : 1-9, 1926.

Zur Theorie der Hæmatoxylinfærbungen. Ein Beitrag zum færberischen Nachweis der Sellipoide. Virchow's Arch. **261** : 846-857, 1926.

Zur Morphologie und Mikrochemie der tierischen Zelle. Nachweis der Zellemembran. ibid. **265**: 805-826, 1925.

Zur Theorie der Desinfektion. Mikrochemische Untersuchungen ueber die Wirkung von Schwermetallen und Farbstoffen auf lebende Bakterien Cbl. Bakt. Orig. **104** : 410-428, 1927.

Wasserlœsliches Phosphatid und Oxydase (Nadi) Reaktion. Bioch. Zschr. **207** : 177-185, 1929.

Zur Theorie der Vitalfærbung. Z ges. Exp. Med. **82** : 480-524, 1932.

Bestimmung der H-Konzentration in der lebenden Hefeund Bakterienzelle. Protoplasma, **17** : 454, 1923.

Ueber die Giftigkeit von Schwemetallsalzen fuer Mikororganismen. Cbl.Bakt Orig. **124** : 572-574, 1923.

Ueber die pH-Zahl der Bakterien, Archiv f. Mikrobiol. **4** : 241-247, 1932.

Die Gramspecifitæt der Desinfektionosvorgænge, ibid. **4** : 248, 1933.

Local anæsthetics, Chemical Products, **12**. No. 6, 1949.

3. Goodman, L. and Gilman, A. : Pharmacological Basis of Therapeutics, New York, Macmillan, 1941.

4. Græfe, V. and Magistris, H. : Zur Ghemie & Physiologieder Pflanzenphosphatide, Bioch. Zschr. **176** : 266-290, 1926.

5. Hauser, E. A. *et al.* J. Phys. and Colloid. Chem. **53** : 287, 1949.

6. Henry, R. J. : Mode of Action of Sulphonamides, Bact. Rev. **1** : 175-262, 1944.

7. Sevag, M. G. *et al.* : Respiration of Streptococcus Pyogenes, Inhibition of Growth by Sulfanilamide, Inhibition of Respiration by Hydroxylamine and Its Sulfonamide and other Derivaties, J. Bact. **43** : 421-447, 1942.

8. Sollman, T. : Manual of Pharmacology, W. B. Saunders, Philadelphia, 1948.

9. Unna, P. G. Chromolyse in Abderhaldens Biologische Arbeitsmethoden, V. T. 2, 1922.

ANTIBIOTICS IN ABDOMINAL SURGERY WITH A CASE REPORT

B. L. Chopra *

With increasing frequency newer Antibiotics are being introduced one after another, some of them with a wider spectrum of therapy than their predecessors and some of them with a selective and specific action as well.

Terramycin, a new antibiotic has been isolated from a soil sample and so named because of the cracked appearance of the growth on agar media. Then there is neomycin, reported to be good for streptomycin sensitive and resistant strains of tubercle bacilli, is more effective than streptomycin against salmonella, *viz.*, Vibrio-cholera. It is less toxic than polymyxin D.

Fradicin, another anti-fungus agent is as effective as aureomycin against gram negative bacilli of coli aerogenes groups and gram positive growths of streptococci.

Of all these antibiotics, penicillin is valuable in abdominal surgery. Satisfactory results have been observed by using streptomycin; the spread of appendicitis has been controlled and the lump has disappeared rather more quickly. Its action on *E. coli* is possibly responsible for its good results. Of course, aureomycin remains the drug of choice in the treatment of peritonitis of appendical origin according to very recent literature. The drug is said to be effective against all forms of organisms giving rise to acute appendicitis. Recently in a case of an appendicular abscess with adherent retrocæcal appendix, I found great benefit wi h a regular course of penicillin injections 50,000 units every 6 hours given for 3 days. The spread of infection was controlled and the appendicular lump was localised to the right iliac fossa. The initial treatment with penicillin was of very great use during the convalescent stage after the operation. The abdomen was opened by a large 5″ long incision. Soon after, a pint of greenish pus was withdrawn. The wound was packed with gauze soaked in penicillin solution and a rubber drainage tube put in. After the operation the man made a much quicker recovery than in those where no antibiotics were given, before antibiotics were available for abdominal surgery. In another case of peritonitis, aureomycin given before opening the abdomen was of great help.

SUMMARY

1. A brief analysis of the place of antibiotics in abdominal surgery is made.

2. It appears that the judicious use and choice of antibiotics before, during and after abdominal surgery, is of considerable help in the speedy cure of the conditions.

3. A case of appendicular abscess treated with penicillin is reported.

---

* Divisional Medical Officer, E I. Railway, Howrah.

My thanks are due to Dr S. S. Kent, M D., Cheif Medical Officer E I. Railway, for permission to publish this article.

FIFTH GUJARAT AND SAURASHTRA PROVINCIAL MEDICAL CONFERENCE 1951

Impressions of a correspondent

The Fifth Gujarat and Saurashtra Provincial Medical Conference was held at Nadiad on March 29th, 30th and April 1st, 1951.

Nadiad, though not the capital of Kaira district, is a very important town in Charotar because of its connecting rail and road links with the interior in all directions.

Nadiad has produced eminent men of letters like Govardhanram Tripathi, author of the well known Gujarati novel 'Saraswati Chandra'. The great poet Nanalal compared this town to Weimar of Germany because it produced a large number of literary luminaries. Sardar Vallabhbhai Patel and his brother, Vithalbhai Patel, had their early education in this town. It has also produced a number of politicians and civil servants who have occupied very high posts in Kathiawar States and Government of India.

Besides, Nadiad has many old historical places and educational institutions which occupy important positions in the whole of Central Gujarat.

Nadiad, with such a historic background and a small branch consisting of twenty-five qualified practitioners ventured to invite a Provincial Conference. The boldness associated with hard work of the organisers made the Conference Session a very successful one. Dr. Ishubhai Patel was particularly mentioned by many as the chief organiser of the Conference.

The President of the Reception Committee, Dr. R. Aldrich, welcomed the delegates and visitors on the opening day at a function which was held in the Town Hall. Dr. C. S. Patel, President of the Indian Medical Council, inaugurated the Conference and made important remarks pertaining to the medical education and population in this country. Dr. M.D. Patel, Prof. of Surgery, B. J. Medical College, Ahmedabad, who was the President of the Conference, in his address, dwelt upon various aspects concerning the improvement of the education, teaching, ayurvedic medicine, rural practitioners and pharmaceutical drugs.

The Conference was held in a specially erected pandal in the grounds of the hostel and adjoining it was a Scientific and Medical Exhibition. The delegates and visitors were accommodated in the houses of the local practitioners and in the hostel. Food was excellent and served in a specially erected 'Shamiyana'. The quality of the food was so good that delegates who had visited a previous conference at Surat—a place famous for its dishes—remarked about Nadiad out-doing Surat. Both the vegetarians and the non-vegetarians were equally pleased and the less orthodox frequently changed the thin dividing line between the two in the dining room and took the advantage of both.

The Scientific Session started in the afternoon with a symposium on Hypertension introduced by Dr. Cook. The session was participated in by a number of general practitioners whose main complain was the lack of attention in this scientific session to the need of the rural practitioner who works unaided by any expert advice or accessory help, like that from laboratory, radiography, etc., which modern medicine can offer. At a symposium on Obstetric Emergency in rural areas, there was a keen discussion regarding the use of pituitrin—pitressin—in delayed labour. On listening to this discussion one sympathised with the rural practitioner in his difficulties and, inspite of all the latest advance which may be available in the text books, recent published literature or personal advice from experts, the rural practitioner still remains the sole judge regarding the condition of the patient and the treatment to be adopted when he is faced with an emergency in a remote inland village. He should intelligently evaluate evidence before him in the case which confronts him. At a symposium on Acute Abdomen, the speakers mostly enumerated the text book conditions without quoting any personal experience. Listeners might as well have taken up a text book instead of listening to such a symposium.

On the last day there were some changes in the papers. There was only one paper in the afternoon, the morning being kept for the Open Session of the Conference. Large number of resolutions were put forward, discussed, amended, amendments rejected and passed. Some of them were of dubious value and could hardly serve the medical profession.

The paper read by Dr. J.M. Pandya of Umreth, on Medical Astrology was the most interesting and stimulating even though it created a great amount of laughter in the audience. If all the practising doctors studied medical astrology, half of their mental worries would be solved by giving a correct prognosis in any difficult and baffling case and they would have the reputation of being always right. It is wondered why there was no resolution passed at the above Conference that medical astrology should be included as one of the subjects in the curriculum of M.B.B.S. He narrated some astounding examples by which he had correctly told the site of disease long before it was evident. As for example, a girl who had a particular planet in her astrology which governs the bones had tuberculosis of the bones confirmed eight months after she started getting fever.

Large number of practitioners attended the Scientific Sessions from surrounding places like Ahmedabad, Baroda, Cambay and other nearby places without being absent from their headquarters for long. Many practitioners from Ahmedabad, Anand and neighbouring places came on Sunday afternoon to listen to the only paper scheduled for the day to be read by Dr. J. C. Patel on the 'Necessity of B Complex in the Treatment of Anæmias' and were disappointed to find that the paper was read in the morning. Such changes in the time-table do not do credit to the organisers of the Conference.

Sight-seeing to Vallabh Vaidyanagar and Santaram and Swaminarayan temples was organised on Sunday afternoon and was well patronised.

However, considering everything, the organisers should be congratulated on the very successful provincial conference when one bears in mind that it was organised by a small branch.

One finds that practitioners attend such conferences more from the point of view of a bus man's holiday and a social meeting of friends whom they have not seen for many years. And, as the years are passing by, one finds more and more people coming to attend these conferences both with a view to learn something and for sight-seeing.

CURRENT MEDICAL LITERATURE

MEDICINE

VITAMIN D TREATMENT OF EXTRAPULMONARY TUBERCULOSIS, Gertler, W.: Journal of Tuberculosis, 94; 288, 1950. 10 illustrations.

The important consideration for the success of chemotherapy is adequate vascularization of the affected tissue and capillary permeability so that the drug is able to reach the affected area in the required concentration. The characteristic tuberculoid tissue structure with granulation and connective tissue is an obstacle to chemotherapy.

Treatment with high doses of vitamin D_2 in lupus vulgaris was first tried in Germany by Jordon following successful treatment in France, Belgium and England for some time. Later on, Vitamin D2 treatment was tried in other forms of tuberculosis. Menschel (1929) praised the great efficacy of high doses of vitamin D particularly in cases of open pulmonary tuberculosis which has been recently confirmed by Heilmeyer. A kind of competition between chemotherapeutic methods and vitamin D arose as to the efficacy in various forms of tuberculosis, but because of their different points of attack, a satisfactory method will probably evolve in a combination.

The advantage of Vitamin D is that it can be given orally and can be taken for years without unpleasant reactions. 813 cases of tuberculosis of the skin were studied in Leipzig Clinic. All cases responded to vitamin D_2. In tuberculosis of the lung calcium was administered. All the patients were on a standard diet nearly salt-free. Two kinds of treatment proved successful: (1) Daily administration of 1 mg. vitamin D_2 for adults was regarded as optimum minimal dose; (2) 10 mg. vitamin D_2 every 7th day or 15 mg. vitamin D_2 every 10th day.

With 1 mg daily dose there appeared a syndrome on the 4th week,—a transitory flare up of skin changes. The syndrome occurs in diminishing degrees in the course of months of treatment. The syndrome does not necessitate stopping of treatment. It retrogresses in 7-10 days and changes to a distinct healing process In four months, one-third of the cases of lupus of the skin and one-half of the cases of mucous membrane, become symptom-free.

With vitamin D3 the healing was accelerated. Some of the patients, however, showed lupoid deposits even after 18 months.

During the first three months there is danger of reactivation of the old lesions of the lung, specially during the syndrome—so careful adjustment must be made of the dosage particularly for the first three months and if there is exacerbation of lung symptoms, the dosage must be reduced. In some cases, treatment must be suspended temporarily. The danger of reactivation is non-existent in later months.

Tuberculosis of the larynx, bones and joints improved after vitamin D treatment. Treatment of joints is better than the old methods.

Pulmonary Tuberculosis. One-third of the patients treated for lupus showed positive lung findings which correspond with German statistics before the war. One-third of the productive type of lung cases (16 of 45) retrogressed with vitamin D_2. In the productive exudative type (16 of 28) showed improvement. In purely exudative ones, the figures are still better (17 from 21). Heilmeyer points out that in highly febrile exudative tuberculosis forms of pulmonary tuberculosis, good results can be expected from vitamin D treatment. Hilar tuberculosis in children improved in nearly all cases (18 of 20).

Initial treatment sometimes produces aggravation, transforming a productive focus to an exudative one and may lead to cavity formation—analogus to the exudative course of healing in various forms of skin tuberculosis, so the initial dose should be small and it may be necessary sometimes even to discontinue for a time, but this danger should not lead to the abolition of vitamin D treatment as in skin cases careful control treatment leads to final success.

Case Reports. All indicate ultimate healing of lung lesions with vitamin D_2. The authors state that their statistics in lung tuberculosis are better because the patients are (1) in a condition of high immunity, (2) careful dosage started below optimum minimal dose and (3) long term evaluation of results—deterioration of condition in first few weeks or months—later improved.

Vitamin D_2 influences pulmonary tuberculosis in every stage. "Healing push" during syndrome may be dangerous to lung-producing cavities, hence the necessity of extremely careful dosage. In this respect, TB I/698, streptomycin and P.A.S. are better.

In combined tuberculosis of the skin and lung, "healing pushes" do not occur simultaneously. Reactivation of the skin may not produce exacerbation of the lung but there may be alternation of both conditions.

In pulmonary tuberculosis, vitamin D_2 in small doses have no effect on skin conditions but optimum minimal dosage for skin may reactivate lung condition.

Some effects noted in treatment with vitamin D_2.

(1) Rise in hæmoglobin; initial fall followed by rise after 4th month;

(2) Leukocytosis;

(3) No serious renal symptoms; only push doses sometimes produced isolated erythrocytes or hyaline casts;

(4) Low blood pressure;

(5) Painful nodules in the chest of males;

(6) Women after menopause start menstruating and have pain in the breasts.

No case of death occurred and the authors think that cases of deaths reported are due to overdosage. In patients with circulatory or renal damage—dosage should be low.

The results of investigations suggest that tuberculin reaction diminishes. For the first few months the patients feel restless and irritable which increases in syndrome time and the patients feel calmer with further treatment. Hence an antiallergic effect on the tuberculous organism might be attributed to vitamin D and is assumed to signify a counteraction against specific and general hypersensitivity—a sympathetic and para-sympathetic phase. The sympathetic phase causes transient exacerbation and the para-sympathetic phase induces healing.

Numerous investigations on vitamin D have produced divergent results, sometimes opposing, which indicate that the experiments were performed in different phases of vitamin D therapy.

With vitamin D, anatomical consideration like fibrous encapsulation and avascularity does not play a role in the healing as compared with chemotherapy.

Vitamin D is a sterol similar to the sex hormones. The sex hormones also act on the central nervous system. There may be an action of the sympathetic and para-sympathetic via the central nervous system.

Vitamin D, unlike chemotherapeutics seems mainly to influence the course of tuberculosis by bringing about a stage of non-specific immunity. The function of vitamin D probably consists in non-specific support, control and acceleration of the course instituted by the body itself. Combined treatment with chemotherapeutic drugs may be useful for shortening the duration of treatment. In tuberculosis ultimate healing depends not on complete destruction of the tubercle bacilli but on changed reactions of the tuberculous organism (body).

Toxic reactions to high doses of vitamin D_2 in extrapulmonary tuberculosis occur but they are reversible. So vitamin D_3 treatment ranks equal to chemotherapeutics known so far.

The authors discuss prophylactic treatment of tuberculosis by repeated push therapy in infancy and childhood.

L. BANERJEE.

PROBLEMS CONCERNED WITH THE HISTOLOGIC DIAGNOSIS OF TUBERCULOSIS OF LYMPH NODES, McDonald, J. R. and Weed, L.A.: Am. Jour. Clin. Path., 21 : 223-233, 1951.

The diagnosis of tuberculosis is frequently based on the histological picture rather than on the demonstration of the *Mycobacterium tuberculosis*. The difficulties of collecting histological material in a state suitable for culture, the numerous culture media and animals that are required and the additional staff that may be necessary for this work, as well as the long lapse of time before results are obtainable, make these procedures tedious and expensive and they are rarely resorted to. However it is well known that numerous chronic inflammatory conditions other than tuberculosis are capable of producing an identical histological picture. It is not so widely appreciated that tuberculosis may frequently not exhibit the characteristic histological picture associated with it. These considerations, together with the fact that tuberculosis is a world wide scourge, the existence of which in any particular case cannot be assumed or disregarded too lightly, make it essential that an accurate bacteriological diagnosis be made in every case.

Three groups of cases selected from a large series show the dangers of histological diagnosis alone.

Group 1. Cases not suggesting tuberculosis histologically but where *Mycobacterium tuberculosis* is isolated on culture.

Group 2. Cases suggesting tuberculosis on biopsy but where other causative organisms only can be grown on culture.

Group 3. Cases suggesting tuberculosis on biopsy but where no pathogens are isolated on culture.

Three main difficulties are encountered :—

1. Selection and mode of collection of material for culture.
2. Obtaining material for culture before extensive chemotherapy or antibiotic therapy is given.
3. The bacteriologic examination of the material.

The first two are countered by previous consultation and co-operation with the clinical staff. The third is an individual problem to be considered in relation to the history, clinical picture, etc., of the particular patient concerned. Any "cook book" routine for adoption in every case is often inadequate, and generally wasteful.

In all "problem" cases, efforts must be directed mainly to the isolation of—

(a) the common infective organisms.
(b) *Mycobacterium tuberculosis*.
(c). the brucella group of organisms.
(d) pathogenic fungi.

It is needless to add that other rarer organisms like the rickettsiæ have to be considered where the clinical picture warrants it. Some useful hints regarding the media and methods used by the authors in each instance are given.

A. NANAVATI.

AN EVALUATION OF BANTHINE IN ULCER MANAGEMENT, McHardy, Browne, Edwards and Mareck. : New Orleans, Med. & Surg. Jour. 103: 380, 1951.

Enthusiasm over the success of total vagotomy in the treatment of peptic ulcer has waned. Medical or chemical vagotomy is frequently referred to, and banthine has been heralded as a means to this end. Banthine is B diethylaminoethyl xanthene-9-carboxylate bromide. Given orally it has an atropine-like action on the postganglionic nerve endings of the parasympathetic system and inhibits vagotonia. Experimentally it has been found to block both sympathetic and parasympathetic ganglions. It is also believed to interfere with visceral sensory afferent impulses. Secretory influence is inconstant, and it is unable to produce a negative secretory response to insulin. However, the authors have found that in their patients it has definitely resulted in inducing gastric hypomotility and reduced secretions. This paper is based on an experience of banthine with 162 peptic ulcer patients.

Dosage. In 82 percent of cases the dosage adopted was 50 mg. at six hour intervals during activity, and 150 to 200 mg. on retiring, and 100 mg. six hourly thereafter. In patients showing tolerances to the drug an increased dose of upto 800 mg. in 24 hours can be given. When the ulcer has healed as demonstrated by radiography, a maintenance dose of one-half the therapeutically efficient dose should be used. Finally a regular nocturnal dose of 100 mg. should be maintained.

Toxicity. In a 12 month follow up and an experience with 162 cases the authors have not met with any serious toxic features. In less than half the patients was there any objectionable salivary suppression. Dilatation of the pupil was rare. Dysuria was rather frequent and could be prevented by voiding urine just before a dose. Pybn's obstruction is accentuated. If gastric aspiration and restricted diet is used with banthine a distinction due to purely œdematous phenomenon will be relieved in 72 hours. Glaucoma is a specific contraindication and the drug should be used with in pyloric and prostatic obstruction. Idiosyncrasy is rare.

Therapeutic results. It is yet too early to give a final verdict but the following effects can be recorded. (1) Pain relief was prompt and complete within 38 hours in most cases. Of 162 patients, 138 were completely relieved and 11 had no relief. (2) Nocturnal waking pains present in 116 patients was aborted in all but 7 patients. (3) Nausea and vomiting present in 86 patients was relieved in all but one.

The patients response to banthine is impressive. They are well pleased. Appreciating the fact that the patients with banthine had no supplemental diet or medication, the authors were impressed with the efficacy of banthine as a therapeutic adjunct to ulcer management. They are reserved about making exaggerated claims because they are aware that a longer follow up is necessary. Chronic ulcers with cicatrization and penetration cannot be expected to heal. Pain relief is usually prompt and dramatic. The drug requires further trial, especially, as in it we have an agent that can control gastric hypertoxicity.

E. J. BORGES.

SURGERY

TREATMENT OF ANKLE SPRAIN WITH SPECIAL REFERENCE TO THE USE OF ETHYL CHLORIDE SPRAY, Price, R. A.: Postgraduate Medicine: 9, 58-60, 1951, 9 references, 2 figs.

The author reviews the treatment of ankle sprain and presents a method which he believes to be the simplest and most effective for most ankle sprains.

He classifies them into two varieties, the complete and the incomplete.

The former, constituting 5 to 10 per cent of ankle sprains, is so severe that one or more of the three lateral ankle ligaments are completely torn through allowing an unusual amount of inversion of the foot, and should be immobilised in plaster for approximately six weeks. The treatment for the incomplete tears is of various types.

Gibney first described adhesive strapping which enabled satisfactory healing but relatively long periods of disability resulted. Fifteen years ago, Leriche, Arnulf and others, introduced an ambulatory treatment with injection of a local anæsthetic into and around the painful area of the ankle. The success of this method however was marred by certain undesirable features such as the infection itself and the risk of contamination and infection of the joint.

The author has used the ethyl chloride spray extensively in the relief of pain and treatment of this injury in army troops. After physical and rœntgenological examination to exclude malleolar fracture, the painful areas are sprayed till the skin is blanched. Massage of the tissues is employed to relieve the discomfort of the cold, after which the patient is told to stand with full weight on the injured ankle, and if pain is still present, a second spraying is given. The ankle is wrapped with an elastic bandage for 10 to 14 days during which time he is encouraged to return to work or regular duty and to return for treatment if pain develops in the ankle. Occasionally a second treatment is necessary, 12 or 24 hours later.

The author finds the results most gratifying and hopes that wider adoption of this method would reduce the morbidity of this common injury.

EUSTACE J. DE SOUZA.

PERITONEOSCOPY—AN EVALUATION OF 396 EXAMINATIONS, Anderson, J. R., Dockerty, M., B. and Wangh, J. M.: Proc. of the Staff Meetings of the Mayo Clinic, **25**: 601-605, 1950. 3 tables.

The authors review the information obtained and the utility of 396 examinations in 392 patients from the first peritoneoscopic examination at the clinic in 1938, where a complete study of biopsy material from 181 examinations was considered the most objective method of determining the value of peritoneoscopy. The microscopic appearance of these specimens was compared with the gross appearance seen through the scope and with the pathologic material and clinical findings obtained in the course of the illness.

When peritoneoscopy was employed to confirm a clinical diagnosis, the correct diagnosis, as established by follow-up, was made by peritoneoscopy in 112 of 120 patients. Peritoneoscopy used to perform a diagnosis from an array of possibilities was useful in 108 of 152 examinations.

It was most useful in the diagnosis of benign and malignant diseases of the peritoneum, less so in diseases of the liver. The accuracy of diagnostic value was greatly increased by removal of tissue for biopsy, but the prothrombin level of the blood should be near normal limits if a biopsy is to be performed on the liver.

The anæsthesia used in most cases was pentothal sodium supplemented with oxygen by mask and occasionally with nitrous oxide.

The authors believe that any case with a doubtful diagnosis with ascites should be examined at least once by peritoneoscopy. Fatalities are not frequent, only one in this series could be attributed to this cause. Those that die following peritoneoscopy do so from the natural course of this disease where it is significant that the mortality is no more than ordinary trocar paracentesis.

EUSTACE J. DE SOUZA.

THE SURGICAL MANAGEMENT OF CHRONIC OSTEOMYELITIS BY SAUCERIZATION, PRIMARY CLOSURE, AND ANTIBIOTIC CONTROL—AUREOMYCIN, Joseph Buchman and John Blair. : J. Bone & Joint Surg., 33A: 107-117, 1951.

The authors give their experience in a preliminary report. They have used aureomycin because of the ease of administration, absence of side effects, and wide range of action. The results are as satisfactory if not better than with the use of penicillin and streptomycin.

Their technique consists of the following: Under general anæsthesia and tourniquet control, an incision is made sufficiently extensive to expose normal bone at the extremities of the lesion and to allow the most direct approach to the diseased area without endangering important blood vessels, nerves, or muscular mechanisms. The soft tissue scar is excised to the greatest extent possible. The periosteum and soft tissues are stripped only from those areas of bone to be excised. Long bones are usually unroofed with a motor saw, and the lesion is saucerised with S-shaped gouges and chisels, normal bone and medullary canal being exposed at the extremities of the lesion. The walls of the saucerised area are levelled off to make a shallow cavity, all visible foci and overhanging ledges are removed. The wound is then thoroughly cleansed and flooded with a solution of saline containing 0.5 mg. of aureomycin per cubic centimetre. The wound is then closed without drainage in several layers wherever possible. When there is insufficient skin for a satisfactory closure, dermoplastic procedure is carried out by undermining the skin and utilising releasing incisions; these incisions may or may not be closed, depending upon the local conditions. Sinus tracts are excised wherever possible. If excision is not feasible, the tracts are curetted and the openings are closed with one or two sutures. Wet dressings containing the antibiotic solution are applied after skin closure. A compression bandage of sheet wadding, flannel, and adhesive, is used to immobilise the limb and to support its circulation. The tourniquet is now removed. Plaster of Paris support is used only when excessive amount of bone has ben removed and post operative fracture is feared.

Antibiotic therapy is started 24 hours before the operation. Every 6 hours 500 mg. of aureomycin is given by mouth. During operation an intravenous infusion of 1000 cc. of saline containing 500 mg. of aureomycin is given. In the post-operative period 500 mg. every 6 hours is continued. The wound is left undisturbed until the tenth post-operative day at which time the sutures are removed. In the great majority of instances, healing by primary intention is found at this time. The line of incision is nevertheless supported with adhesive ridges because fluctuation is still evident in the superficially closed wound. It is most important that the underlying hæmatoma be not discharged. Evacuation of the hæmatoma results in the formation of a cavity which can only be healed by granulations, thus defeating the objective of healing by primary intention. If partial evacuation of the hæmatoma occurs, the wound is covered with a dry dressing. At no time is the wound probed, drained, or irrigated. Healing occurs, although it may be delayed for several weeks.

E. J. BORGES.

THE RADICAL CURE OF INGUINAL AND FEMORAL HERNIA WITH A POLYTHENE INSERT, Thompson, W. : B.M.J. 1 : 797-799, 1951.

The author used polythene repair in 61 out of 103 herniorrhaphies in a series of selected cases contaning only those which required major repair. The object, which was to reduce the recurrence, morbidity and mortality in different herniæ to nil was achieved in all but one case where a persistent sinus led to removal of the polythene insert.

The polythene has the advantages of being, light, cheap, water repellant, easily cut with a scissors and perforated with a needle, and is best sterilized by soaking in perchloride of mercury 1:1000, biniodide of mercury 1:1000 or lysol or dettol.

The author prefers the combined repair where the incision is made along Langers tension lines, beginning over the outer third of Pouparts ligament extending to the external ring, the skin flap is reflected downwards exposing the inguinal and femoral rings. The polythene plate cut to shape is placed in the extra peritoneal fat, the lower border is fixed by stitching it medially to Coopers ligament just behind the insertion of the conjoint tendon into the pectineal line, and laterally to the Pouparts ligament opposite the deep epigastric vessels.

The upper flap of the transversalis fascia is brought down and sutured to the Cooper's ligament, the Gumbernat's ligament, the deep femoral arch and the Pouparts ligament. Because of the rather extensive dissection required, good relaxation is essential. Early ambulation is effected and after six weeks convalescence, return to light duties and after three months full duties are resumed.

EUSTACE J. DE SOUZA.

SURGICAL TREATMENT OF CLUBFOOT, McCanley, J. C. Jr.: Surg. Clin., N. America 31 : 561-573, 1951. 32 references, 3 figs.

It is important to recognise the wide variation of problems with the general pattern. The commonest type is found in otherwise normal infants and not associated with other congenital deformities. There are other types which are a part of a more profound congenital disturbances, *i.e.*, associated with arthrogryphosis multiplex congenita,or the type in conjunction with spina bifida and others of neurogenic or myogenic origin, and these are more resistant to any form of treatment.

Effective therapy can only result from a well planned system of treatment which should begin in early infancy and continue with uninterrupted after-care and observation throughout childhood.

The standards of correction must be rœntgenological rather than the clinical appearance of correction. Kite has called attention to the alignment of the long axis of the talus and the first metatarsal.

The author considers the following general indications for treatment :—

Younger age group—up to 6 years.

1. Incomplete equinus correction with satisfactory varus correction.
2. Incomplete varus correction with or without satisfactory equinus correction.
3. Persistent functional varus.
4. Persistent intoeing.

Older age group—8 years and older.

5. Complaints and disability associated with persistent deformity.

Operative treatment of equinus. This is indicated if proper stretching force fails to correct the equinus relationship of the hind foot, if the varus component is corrected and if there is sufficiently strong calf muscle to survive functionally in the lengthened position. It is contraindicated in rocker foot, uncorrected varus and structural deformity preventing upward rotation at the ankle. The author prefers the open operation of tendon lengthening.

Operative correction of varus—Younger age group. The author prefers a soft tissue release operation which is indicated if adequate conservative correction fails, if there is tendency to recurrence or if the treatment in infancy was inadequate, and in clubfoot of neurogenic or fibrodysplasic origin. It is contraindicated in functional varus that is correctable by manipulation, in the too young or too old and in structural deformity preventing adequate correction. The optimum age is from three and a half to five and a half years.

Anterior tibial muscle transplantation is used in functional varus correctable by manipulation.

Derotation of the leg bones is used in unusually persistent adduction of the foot where there is rotation or torsion of a corrected foot on the thigh.

Surgery in the older age group—over 8 years. Sub total or triple arthrodesis is used in persistent deformities where subjective complaints or disability is present or inevitable, where previous operative correction has failed or to correct a varus and equinus where the talus has matured in a position of plantar flexion so as to prevent any dorsiflexion.

EUSTACE J. DE SOUZA.

EOSINOPHILIC GRANULOMA OF BONE, Henderson, E.D., Dahlin, D. C. and Bickel, W. H.: Proc. of the Mayo Clinic **25**: 534-541, 1950. 13 references, 2 figures.

The authors describe this condition which was unrecognised till 1940 when Otani and Ehrlich described what they knew of "solitary granuloma of bone". Lichtenstein and Jaffe presented a similar destructive lesion but called attention to the large numbers of eosinophilic leucocytes in the sections. It is established as a condition where a destructive lesion of either a long or flat bone involves the cortex and may invade the surrounding tissues, with a short history of pain at the site of the lesion with or without swelling. It tends to occur in children and young adults with no systemic reaction and readily responds to curettage or rœntgen therapy.

The bone is replaced by tissue resembling granulation tissue, and consists of histiocytes arranged in sheets, with variable numbers of eosinophilic leucocytes, areas of hæmorrhage and necrosis.

Green and Farber pointed the similarity to Hand-Schüler-Christian disease and thought it a variant of the lipoid dystrophies. Thaunhauser finds no justification for this assumption while Teilum and others thought eosinophilic granuloma an early phase of the Hand-Schuler-Christian syndrome. The authors first attempted to distinguish the two conditions on histopathologic grounds alone and fixed certain criteria for differentiation.

Large numbers of foam cells or lipophages indicated a diagnosis of Hand-Schuller-Christian disease as also the presence of mature or polymorphonuclear eosinophils, while indented or bilobed nuclei of eosinophilic leucocytes were to indicate eosinophilic granuloma. The presence of lymphocytes, plasma cells, hæmorrhage and necrosis, substantiated the latter diagnosis. With these criteria, 14 cases were studied and only in 1 could a diagnosis of Hand-Schuler-Christian disease be made. Studying the history and clinical course, 4 more cases could be put in the category of the Hand-Schüler-Christian disease. In one, the diagnosis was doubtful or borderline, in the remaining 8 the conditions for eosinophilic granuloma could be fulfilled.

Clinically, the presence of significant anæmia was a grave prognostic sign. Exophthalmos, diabetes insipidus, multiple lesions of the skull or visceral lesions, indicate the graver Hand-Schuller-Christian disease. Eosinophilic granuloma carries an excellent prognosis and a predictable course, and the authors feel that this diagnosis should be made only in cases with no visceral lesions and if not more than two bony lesions are present at the same time.

They did not find any conclusive relationship between this condition and the lipoid hystiocytoses and found no evidence to support the claim that it was an early phase of Hand-Schüller-Christian disease.

EUSTACE J. DE SOUZA.

THE APPROACH TO SURGERY AND ANAESTHESIA IN OLD AGE, Rudd, T. N.: The Pract. 166: 159-165, 1951. 10 references.

The author is of the opinion that the elderly receive far too little rather than too much treatment, because of an extreme conservatism. He feels however, that with modern methods a larger number can now be judged fit for surgery because experience of geriatric surgery shows that wounds heal well and the incidence of pulmonary and thrombotic complications is not as overwhelming if the patient is mobilised early and that the senile heart stands anæsthesia well if shock is avoided. The patients full co-operation is essential as without it no surgical treatment except in gravest emergency should be considered.

Pre-operative Investigations. A functional assessment of the body as a whole and of each system separately should be the basis of a complete physical examination.

Blood counts are essential as anæmic patients tolerate surgery poorly and their wounds heal slowly. Surgery is seldom advisable with a hæmoglobin level lower than 70 per cent, in which case, a small transfusion raises the plasma protein level as well as the hæmoglobin. Some geriatric surgeons (Steiglitz 1949) recommend it routinely. If a transfusion is not available and the operation not an emergency, intravenous iron and oral iron help in raising the hæmoglobin.

The fasting blood sugar estimation is invaluable in detecting those diabetics without glycosuria which is not uncommon in the elderly.

Blood urea and non protein nitrogen, if raised, suggest the more careful examination of renal function. Short hospital rest and treatment of anæmia if present often produce marked improvement of renal function.

The routine urine examination, mesurement of daily output and specific gravity of the twenty-four hour sample, should be carried out in every case.

As a preliminary to surgery the patient should be mobilised as much as possible before operation.

Anæsthesia in the elderly. Rowntree (1931) stresses the point that the anæsthetist is more important than the anæsthetic used. A sympathetic anæsthetist who is willing to take into consideration the opinion of the geriatrician, will rapidly become a safe and kindly anæsthetist of the aged, if he recognises the importance of the hæmoglobin level and light premedication. Cyclopropane is much favoured by some, though simple gas oxygen and ether give excellent results with or without CO_2 absorption.

Refrigeration anæsthesia must not be forgotten in gangrene or other conditions requiring amputation of a limb, as it makes surgery possible in the hopelessly debilitated or septic cases with almost complete absence of shock, or constitutional disturbance. With proper technique, the limb can be moved, skin grafts can be applied without pain and post-operative pain is minimised.

Surgical procedures. The scope can be vastly increased with proper experience; a wider field for the performance of prostatectomies in the very old makes for greater comfort for those who were previously condemned to the dangers and discomforts of the supra-pubic tube. Disabling herniæ uncontrollable by trusses, can now be dealt with in the seventh and eighth decades. Certain broad principles must be clearly followed. Shock must be minimised by lightness of touch and the avoidance of hæmorrhage. Procedures must be adapted to suit the requirements of the age group dealt with, and the aim of the surgeon should be the completion of the operation within an hour.

After treatment. When the effects of anæsthesia wear off, then the stormy period begins; careful preparation must make this stage smooth and uneventful.

Mental confusion is to be expected, and a confusional state due to the drug must be thought of.

Careful nursing must anticipate the discomfort of a full bladder or bowel.

Kidney function must be conserved by a thorough understanding of the principles of salt and water depletion.

Venous thrombosis must be obviated by early mobilisation, deep breathing and if it does occur dicoumarol can be administered under proper direction and control.

The healing of wounds especially of the extremities in arteriosclerosis may cause anxiety. Here the massive dose administration of Viamin E is worthy of trial, when the dose should be 200-300 mg. daily for 4 to 6 weeks or longer. Iron salts are contraindicated in this regime and insulin requirements are modified, as hypoglycæmia tends to occur. Thyrotoxic heart disease contraindicates Vitamin E therapy.

EUSTACE J. DE SOUZA.

IMMEDIATE UNTOWARD REACTIONS TO SPINAL ANAESTHESIA, Dwyer, C. S.: Amer J. of Surg., **81**: 172-177, 1951. 1 fig. 11 references.

The author feels that as most deaths are preventable it is wise to discuss the abnormal physiologic mechanisms and the treatment of these untoward reactions so as to avoid a fatal outcome.

He condemns any routinisation of method, and stresses the need for proper selection and the mastery of a single technique rather than an experimentation with several. Constant vigilance and proper equipment for resuscitation are absolutely essential.

The more common causes are discussed individually.

Uncontrolled Height of Anæsthesia. Though cephalad spread is usually studiously avoided, it is liable to occur in patients with increased abdominal pressure, from obesity, ascites, pregnancy or tumours. In such case alternate methods like fractional spinal or endotracheal inhalation anæsthesia are safer for abdominal surgery.

The intercostal and finally the phrenic nerve roots being involved, cessation of respiration may be sudden but often, unless too heavily narcotised the patient gives some warning, a feeling of "numbness" all over, cyanosis or a weak hoarse voice or slurred speech. Death follows in a few minutes if immediate and proper treatment is not forthcoming, which consists in a free air-way, artificial respiration, and oxygen. If circulation is adequate one need only wait for the level of paralysis to recede.

Peripheral Circulatory Failure with Cerebral and Medullary Hypoxia. This is the commonest cause of death. Though more common with high spinal analgesia, the level is not the basis for it. The sympathetic vasomotor fibres are so quickly anæsthetised that circulatory collapse follows abruptly after the sub-arachnoid injection. Dehydration, chemical imbalance, anæmia and shock invite hazardous blood pressure levels, as also marked hypertension and hypotension.

The cause is one for speculation but appears to be due to paralysis of the segmental sympathetic vaso-constrictors in the anterior nerve roots with increased capacity of the vascular bed, leading to diminished venous return and diminished cardiac output. The efficacy of the carotid sinus reflex and aortic sinus reflex is greatly diminished by the sympathetic vasoconstrictor paralysis in the anæsthetised area. Hypoxia leads to stimulation of respiration which is later depressed and may finally cease from central failure. Warning signs should be recognised at once. The patient may yawn, and appear quite sleepy. A talkative patient may become quiet. The face becomes expressionless and fixed. He may complain of nausea, or excessive sweating. Pallor and cyanosis appear as peripheral circulation fails.

Intravascular Injection This is very rare and the reactions are of two types. In the neurological type there is cerebral stimulation noticed by talkativeness, excitement and convulsions; treated by oxygen inhalation, artificial respiration if necessary and short acting barbiturates.

The circulatory type is evidenced by a fall in blood pressure, pallor, sweating nausea and vomiting and air hunger, and is treated by oxygen administration artificial respiration if necessary, intravenous analeptics such as epinephrine or ephedrine and intravenous fluids.

Drug Sensitivity. Though rare, if a patient has had a reaction to local procaine, it is judicious to test the agent intracutaneously. A control wheal of a solution of physiologic saline is made on the forearm and of a 1 per cent procaine solution or dilute solution of other suspected drug, is made nearby. After 5 minutes any indications of sensitivity are noted.

Often the sensations of faintness, palpitation, dyspnœa, tremors and nervousness during local anæsthesia are due to the vasoconstrictor drug in the anæsthetic solution which may be tested by subcutaneous injection of a minute dose of the vasoconstrictor, when the patient will complain of similar symptoms if the test is positive.

Action of the Drug directly on the Medullary Centres. Though this has been considered by some as the basis of untowards reactions, it has been shown by Kosker that extremely high concentrations of anæsthetic drugs must be applied directly to these centres to bring about paralysis.

Reactions which may or may not be associated with or be secondary to the method. Here sudden deaths give very little time to correctly evaluate the cause and only autopsy will confirm the real cause.

EUSTACE J. DE SOUZA.

CARCINOMA OF THE CERVIX UTERI IN IDENTICAL TWINS, Stocking, B. W.: Cancer, 3: 969 971, 1950.

A case is reported of Doris P., a bookkeeper aged 34 years who was examined for continuous vaginal bleeding. A fungating mass on the vaginal vault was subjected to biopsy and was diagnosed as a squamous cell carcinoma grade 3. The twin sister, Doloris F. was then brought for examination at the instance of an older brother, a physician. She had no complaints. A "cervical erosion" was found, subjected to biopsy and diagnosed as a squamous carcinoma grade 3. Doris. P., being an advanced case had an unfavourable course and died after 2½ years Doloris F. made an uneventful recovery. A brief outline is given of the treatment followed in each case.

The sisters belonged to a family of eight children. None of the others were twins. The mother had four sisters (2 pairs of twins), and two brothers. There-were no twins in the father's family. There was no history of cancer in either family. The two patients were born with a common placenta and were remarkably alike in appearance, suggesting that they were monozygous.

The question of the simultaneous occurrence of a disease or a tumour in both identical twins has long fascinated students of heredity and of cancer. There is, however, no report in English of a detailed study regarding the occurrence of neoplasms in a large series of unselected twins, and the question appears to be still unsettled. A bibliography of the literature on the subject is given by the authors.

A. NANAVATI.

PEDIATRICS

PERTUSSIS—CLINICAL COMPARISON OF THE NEWER ANTIBIOTICS, *Booher, C. F.*, Farrell, J.D., Vest, F. J. : J. Ped, 38 : 411-422, 1951, 11 figures and 27 references.

The authors studied the comparative clinical effects of aureomycin, chloromycetin and terramycin in 111 cases of uncomplicated pertussis and also attempted to determine the effective minimal dose for these drugs. In all children who were included in this study, two of the following three criteria were present :—(1) isolation of H. Pertussis organism, (2) leucocytosis with absolute lymphocytosis, and (3) observation of typical paroxysmal coughs by two or more qualified observers.

36 cases were treated with chloromycetin and out of these success was reported in 34. The whoop stage shortened to 5.5 days as compared to 13 days in the controlled group. The temperature dropped rapidly to normal. There was a fairly rapid lessening in the general toxicity. The average total length of the disease showed only a slight change from the controlled group. The average total drug required to achieve satisfactory clinical response was 5.5 Gm.

Aureomycin was given to 22 children in a dosage of 50 mg. per kilogram body weight for 24 hours and there was shortening in the duration of the whoop stage of the illness but the average duration of the cough stage and the period of hospitalisation were unaltered. The temperature elevations were more persistent.

Terramycin was successful in 38 out of 41 patients. The drug was given in the standard dose of 50 mg. per kilogram body weight. There was a shortening in the whoop stage by 8.4 days as compared to the controlled group. The temperature dropped rapidly and the toxicity improved. The cough stage was lessened only slightly. The rectal route was used in three patients and in them the dosage was increased by 25 per cent. The authors feel that terramycin has a definite place in the treatment of pertussis.

5 cases were treated with a combination of these three anti-biotics but there was no substantial clinical change when compared to the results obtained by administration of the drugs singly.

The authors could not find any difference in the course of the disease between those who were immunised and those who were not immunised. In patients treated with streptomycin and aureomycin there was prolonged temperature for which the authors were not able to suggest an explanation. In the chloromycetin and terramycin cases there was a prompt and rapid decline of temperature to normal.

G. COELHO.

TERRAMYCIN IN THE TREATMENT OF PNEUMONIAS OF CHILDHOOD, Wooding, C. H., and Scott, R. B.: J. Ped., 38: 423-427, 1951.

The authors treated 10 children of bacterial pneumonia, 6 of whom were suffering from lobar pneumonia and 4 from broncho-pneumonia with terramycin. They had been ill for an average of four days prior to the administration of the drug. All of them received the drug orally suspended in a syrup vehicle. All but one accepted the drug well. In the 9 cases which took the drug well, the temperature was normal immediately in two patients, in one day in one, in three days in two, and in four days in one. The X-Ray picture cleared in four days in one, in five days in four, in six days in one, in 8 days in two and in fifteen days in one. The last case had broncho-pneumonia as a complication of H. Pertussis infection. This small study indicates the value of terramycin in the treatment of pneumonia. The advantage of terramycin is in its wide anti-microbial spectrum which includes coccal, bacterial and viral agents. Further it is effective when given orally.

G. COELHO.

SUBDURAL EFFUSIONS COMPLICATING BACTERIAL MENINGITIS, Smith, M.H. D., Dormont, R. E. and Prather, G.W.: Pediatrics, 7: 34-43, 1951.

The authors present data on the incidence, etiology, clinical manifestations, pathogenesis and therapy of subdural effusions occurring after bacterial meningitis. Subdural effusions have until recently been overlooked as sequelæ of meningitis.

The authors detected subdural effusions in 20 of 43 patients under the age of 2 years admitted for bacterial meningitis due to various causes and adequately treated depending on the etiology by combinations of various therapeutic agents (tuberculous meningitis and a few undiagnosed meningitides excluded); it is probable that more may have had subdural effusions as subdural taps were not performed in the other 23 cases. The age incidence was highest between 3 and 9 months; it is not known how often subdural effusions were present in older patients as subdural taps were performed only in those with open fontanelles. Most of the subdural effusions were discovered a fortnight after the onset of symptoms of meningitis. Trauma incidental to subdural taps could not be held responsible for the development of subsequent subdural collections of fluid, as in 15 of the 20 cases fluid was obtained at the first tap. Indications for subdural taps were varied; in 11 cases, one or more of the following were present, convulsions and focal neurological signs, persistent fever, chronic meningitis, opisthotonus, bulging fontanelle, projectile vomiting and enlarging head; in 9 cases, fluid was discovered on 'routine' tap.

Taps were performed in each patient at first at the two lateral angles of the anterior fontanelle, later only on the side where fluid had previously been demonstrated. The amount of fluid removed varied from 2 cc. to more than 60 cc.; most often it was xanthochromic. The protein and sugar contents of the subdural fluid were usually higher than that of the spinal fluid obtained simultaneously: the protein lay between 50 and 1000 mg./100 c.c., the sugar between 33 and 184 mg./100 cc. In 3 cases, culture of the subdural fluid was positive.

The treatment of this condition is to do subdural taps repeatedly, which the authors had done in all but one of their cases, until either no further fluid could be obtained or the fluid decreased to very small amounts and the patients seemed clinically improved. Amounts as large as 60 to 75 cc. were removed on several occasions without untoward reactions. Two cases were operated upon, their case histories are given in detail. The authors believe that subdural taps should be performed on admission for diagnostic purposes whenever the patient has been treated with antibiotics and has no organisms in the spinal fluid when first seen, as well as in all patients who give evidence of prolonged signs and symptoms of meningitis and in older patients whose convalescence from meningitis is slow or accompanied by prolonged fever or suggestive focal neurological signs.

F. A. NAZARETH.

ACUTE THROMBOSIS OF THE FEMORAL ARTERY IN AN INFANT, Feldman, S. *et* al,: J. Ped., 38: 498-501, 1951.

The etiological factors of this condition have been summarized as the following:

1. Sepsis from fulminating infections which cause pyaemic dissemination leading to thrombotic processes or embolism from septic cardiac vegetations.
2. Trauma, from birth injury or pressure, as for example, gangrene of an extremity due to an encircling, constricting umbilical cord; or accidental puncture of the femoral artery during femoral venoclysis.
3. A typical closure of the ductus arteriosus leading to thrombosis within the duct with protrusion and fragmentation of the clot and subsequent dissemination into the peripheral circulation.
4. Umbilical artery thrombosis: The thrombotic process which closes the umbilical arteries may rarely extend into the hypogastric, iliac arteries and even into the lower end of the aorta.
5. In newborn infants requiring resuscitation, accidental injection of nikethamide into the umbilical artery instead of the vein with retrograde flow into the hypogastric artery causing prolonged arterial spasm with secondary thrombosis.

The treatment should include the following:

1. Sedation for pain which is usually present; since the emotional factor increases the vasospastic element, drugs which cause vasodilatation will help. Papaverine is ideal for vasodilatation but relief of pain is not so dramatic, hence demerol (pethidine) is the drug of choice.
2. Paravertebral sympathetic nerve block is a valuable procedure as by interrupting the reflex arc it relieves vasospasm, allows maintenance of collateral vascular bed and relieves pain.
3. Protection of the limb from infection and trauma by wrapping the limb in gauze and absorbent cotton.
4. Elevation of the head off the bed to augment arterial blood pressure helped by gravity towards the periphery.
5. Anticoagulants' using heparin for immediate effect and at the same time dicumarol; heparin is stopped when the therapeutic effect of dicumarol is attained as reflected in the prothrombin time determination.
6. On no account should heat be applied in any form as it will place an extra-burden on the already deficient circulation and accelerate the appearance of ulceration and gangrene.
7. The presence and spread of infection and onset of toxic symptoms may require radical surgical intervention.

The authors describe a case of a child 1 year old, admitted for lipoid nephrosis, who developed signs of thrombosis of the femoral artery following removal of blood from the femoral vein for investigation. According to the authors, the pathological process leading to thrombosis in this case was injury to the arterial wall producing either mural hæmorrhage and then intraluminal thrombosis or intense vasospasm with secondary thrombosis. The child was treated on the lines suggested above with remarkable recovery, no surgical interference being necessary.

F. A. NAZARETH.

AN EVALUATION OF A CARBOHYDRATE-PHOSPHORIC ACID SOLUTION IN THE MANAGEMENT OF VOMITING, Bradley, J. E. *et al.* : J. Ped., 38 : 41-44, 1951.

The authors report a novel approach to stop vomiting by the use of Emetrol (Kinney & Co.). Emetrol has a pH of 1.5 to 1.6 and is a solution of invert sugars and orthophosphoric acid with suitable stabilizers and flavors.

The solution was tried in 246 cases. 172 cases diagnosed as epidemic vomiting were given 5 cc. doses, undiluted, at intervals of 15 minutes for a total of four doses: older children were given 10 to 15 c.c. at the same interval. The treatment was supplemented by maintaining a low-fat, high-carbohydrate, low-residue diet with elimination of milk and fruits for 24 hours; since there must be no alteration in the pH of the solution before reaching the stomach, it must be given undiluted and for the same reason not immediately followed by water, milk or other liquids. All these children were promptly cured, often with a single dose. Vomiting was likewise controlled in 29 of 43 cases of regurgitation of infants who had failed to respond to barbiturates, atropine or other drugs; the dose used was 2.5 to 5 c.c. fifteen to thirty minutes before feeding. Vomiting was also controlled in 15 of 17 cases of toxic vomiting or vomiting associated with acute infections. All 11 cases of motion sickness were cured; these children who experienced nausea or vomiting as a consequence of automobile riding were given 5 to 10 c.c. before starting a trip and repeated at hourly intervals if the travel was of long duration. The use of this solution does not eliminate the need for correcting improper feeding methods, nor does it correct vomiting due to obstruction as shown in 3 cases of pyloric stenosis in none of whom vomiting was controlled.

F. A. NAZARETH.

THE SIGNIFICANCE OF DELAYED DEVELOPMENTS IN THE DIAGNOSIS OF CEREBRAL PALSY, Denholl, F., and Holden, R. H. : J. Ped., 38 : 452:-456, 1951.

Using the following developmental items, erection of head from prone, reaching for objects, crawling, sitting without support, prehension grasp,, single words, standing alone, crawling alone, two-word or three-word sentences, the authors analysed the records of 100 cases of cerebral palsy children.,

The normal infant can usually lift his head upward from prone position by the end of the first month. Out of 74 children studied 14 per cent could hold their heads erect momentarily by one month, 18 per cent by three months, while the majority failed to hold their heads till much later. Out of 28 cerebral palsy children, 3 per cent reached for objects before five months, which is the age for normal infants, 86 per cent reached for objects later than this, while 11 per cent never reached, at all. Out of 73 children, 15 per cent could sit without support by 8 months (normal for a healthy infant), 14 per cent by 10 months, while 71 per cent did not acquire the ability to sit independently until after 10 months. Whereas the normal infant could crawl by 7 months of age, of 54 cerebral palsy children, only 2 per cent acquired this skill by 8 months, 37 per cent crawled after this age and 61 per cent never crawled. Of 16 cerebral palsy children, 9 acquired prehension by 9 months (normal age for a healthy infant) while the remaining 7 were delayed till 7 months. Of 65 cerebral palsy children, 11 per cent said single words by 9 months (normal age) 15 per cent by ten months, and 74 per cent were delayed beyond 12 months. Of 43 cerebral palsy children, 11 per cent stood alone by 12 months, 2 per cent by 13 months (normal age), while 18 per cent did not stand alone much after this period. Of 57 cerebral palsy children 7 percent walked alone by 15 months, 16 per cent by 18 months (upward limit for normal infants) while 77 per cent walked only after 18 months. Of 39 children, 31 per cent talked in single words by 24 months (normal age), 23 per cent by 30 months; while 46 per cent did not talk until after 30 months.

G. Coelho.

RETROLENTAL FIBROPLASIA, Exline, A. L. and Harrington, M. R.: J. Ped. 38: 1-7, 1951.

Retrolental fibroplasia is manifested by a series of ocular changes leading gradually to a dense white vascular postlenticular opaque membrane occurring in 10 to 30 per cent of infants weighing 3½ pounds and less at birth. The authors followed 80 infants who weighed less than 3½ pounds at birth, and re-examined them after the age of 7 months; no evidence of retrolental fibroplasia was found in any one of them. They discuss the probable etiological factors of retrolental fibroplasia and how management of premature infants in the light of these factors may lower its incidence.

Among the several etiological factors, not a single one appears to stand out. Suspicion has been cast on the use of high potency, water-soluble, multivitamin preparations; the authors did not use these, though they did use vitamin C in increasing amounts to 100 mg. daily by the fourth day, and vitamin D started at 7 to 10 days in increasing amounts from 5,000 to 11,250 USP units daily by the age of 2 weeks. Excessive vitamin A and iron supplements by aggravating vitamin E deficiency may cause retrolental fibroplasia; no vitamin E was given by the authors, even though 15 mg. of elemental iron daily was given from 2 to 4 weeks of age in 61 infants. Hypoprothrombinemia by causing hemorrhage within the eye, and anæmia, have been suggested as etiological factors; 2.4 mg. of a vitamin K precursor and transfusions for hemoglobin levels below 10 Gm. per 100 cc. were a routine practice. Sublethal anoxia has also been suggested as a probable cause; oxygen was liberally used for all the infants included in this study. The authors found no evidence to suggest that climate, geographical distribution, racial factors, poor maternal nutritional status, light, silver nitrate used in conjunctival irrigation, or the use of penicillin or sulfadiazine, were likely contributory factors. Deficient placental transfer of substances which might ordinarily be transferred through the placenta late in pregnancy has been proposed as an etiological factor; this is hard to evaluate; the authors' cases were fed artificially and therefore could not receive hormones or antibodies from this source.

The authors consider dehydration and consequent excessive weight loss during the period of initial neonatal weight loss as a possible contributory factor; they therefore commenced routine feedings at 12 hours and tried to minimize neonatal weight loss. On this regimen, the majority of their cases lost less than 10 per cent of birth weight; 58 per cent had regained birth weight within two weeks.

F. A. Nazareth.

DERMATOLOGY

DISCUSSION OF TATTOO REACTIONS WITH REPORT OF A CASE SHOWING A REACTION TO GREEN COLOUR, Rostenberg, A. and Brown, R. A., et al: Arch. Derm. & Syph, **62**: 540-547, 1950.

While reporting an interesting case of reaction to tattoo marks, the author incidentally discusses possible types of reactions to such procedures. The two main divisions are (1) reactions incident to the tattooing process, *i.e.*, various infections transmitted through the procedure (2) reactions to deposition of foreign material, *viz.* (*a*) development of locus minoris resistance so as to predispose it to the localization of various skin diseases as psoriasis,. lupus erythematosus and lichen planus, etc., (*b*) foreign body type reaction to tattoo ingredients and (*c*) development of allergic sensitization to one of the introduced colours.

The author's patient exhibited the allergic reaction to the green colour of tattoo marks, performed 8 years ago. The patient had generalised atopic dermatitis for the last 6 months, and in the tattoo area the dermatitis restricted itself to the green part only, leaving the red and blue areas unaffected. The histopathologic examination of a biopsy section of the green part conformed to an allergic reaction in that there was predominant infiltration with eosinophilic cells in the midcorium.

Reviewing the literature the authors find reports of cases of allergic reaction to cinnabar used to produce the red colour. Patch tests to cinnabar were positive in several cases. Evidently the authors' case was the first to be reported for reaction to green pigment, the chemical nature of which, they unfortunately, could not decide. The interesting and unusual feature of the case is that the allergic reaction occurred 8 years after the tattooing was done and that too to green pigment, so far unreported in the literature.

An appendix of pigments or dyes used to produce different colours in tattoos is given at the conclusion of the article as under following heads.

Colour	*Chemicals used*
(1) Black ..	.. Carbon with phenol in ammoniacal solution.
(2) Blue ..	.. Cobaltous aluminate.
(3) Brown ..	.. Ochre (ferric hydrate and ferric sulfate and silica, etc.)
(4) Flesh ..	.. Ironoxides.
(5) Green ..	.. (*a*) Chrome oxide green.
	(b) guignet's green.
	(*c*) phthalocyanine dyes (usually copper salts).
(6) Red ..	.. (*a*) cadmium selenide.
	(*b*) cinnabar (Hgs.)
	(*c*) sienna.
(7) Violet ..	.. Manganese violet probably $NHg\ MN_2\ (P_2\ O_7)_2$
(8) White ..	.. (*a*) Titanium dioxide (*b*) zinc oxide.
(9) Yellow ..	.. Cadium yellow ochre.

T. K. MEHTA.

INCOME TAX DISCRIMINATION, Dickinson, F. G.: J. A. M. A., **142**: 1357-1360, 1950. 5 references.

The author compares the status of a physician regarding the income tax laws about his cost of training, expenditure on business and provision for pension, to that provided by companies for its employees. A company can get exemption as business expenses. What it uses for providing of pensions are not taxable till they are received by the employee. A doctor employed by the company can enjoy this benefit but not the individual practitioner. Thus there is an individual discrimination which is particularly burdensome to professional men who practice as individual proprietors and partners. In this article the author quotes section of Federal (U.S.A.), laws for internal revenue and tries to prove that laws should be altered so as to benefit professions—lawyers and particularly doctors. He works out that before the age of 28 when the doctor is about to earn he has already spent $35,000, which he has to repay as compared to another man who started earning at the age of 18. This is his capital investment. He must earn $2,200 to pay for interest (4 per cent on the above capital investment = $1,400) and a premium of $800 for an endowment policy. In addition he must pay for his operating expenditure which is about two fifths of his gross income. The amount of income tax will vary with his income and it can be anything. Hence a physician should have $5,000 per year as minimum allowance in terms of gross income to amortize a capital cost of $35,000. Hence the first income of $5,000 of gross income of a doctor should be excluded from the income tax in comparison with the earning of a person whose earning period started at the age of 18.

Before the World War II the income of an average doctor in active private practice was between $5,000 and $5,200. After the World War the fees of the doctor have increased to 130 as compared to consumer's price index of 159. Thus from the standpoint of doctors, the prosperity has not benefited him as compared to the general public. Ninety per cent of doctors are individual practitioners and can be described as small retailers of professional services and all net income derived by private practice by a doctor is fully subject to current federal income taxes.

The doctor's case is that he undergoes a long training at a high cost, his earning period is short and is bunched in small peak years. He is placed at a higher income tax bracket and hence pays more income taxes during his life time than another person who receives the same life time income spread more evenly over a greater number of years. If he is an employee he gets a relief for an employee pension which is not taxed till he receives it. But since he practices as a single proprietor or partner and not as an employee he is subjected to income tax discrimination in this matter of pensions. The American Medical Association proposes to make a representation to, to appropriate authorities to amend the act, so as to remove the discrimination against doctors particularly for provision for maximum pension. Author then goes on to suggest the way how it can be done in U.S.A.

Whatever has been said by the author in the above article, has been endorsed by the editor in an Editorial. The conditions under which a professional man operates in India is no way different to that in U.S.A. Indian medical association should think of taking up the question of relief in income tax in this country particularly because of high level of taxation here.

J. C. PATEL.

Indian Journal of Medical Sciences
(INCORPORATING THE MEDICAL BULLETIN)

VOLUME 5 SEPTEMBER 1951 NUMBER 9

COPYRIGHT BY THE INDIAN JOURNAL OF MEDICAL SCIENCES

INTRAVENOUS IRON THERAPY (FERRIVENIN BENGER)†

Gurbuxsh Singh.*

HISTORY OF IRON

It would be interesting to trace the history of iron administration for medicinal purposes which is very fascinating and dates from early Greek civilization. Amazingly the metal was introduced as a therapeutic agent as a result of the simple association of ideas in the minds of men that iron meant Strength and Protection. Hence they argued that it would be of value to those who suffered from weakness regardless of its cause. Greeks of that early age thought that Mars had imbued iron with force and properties of the Vehicle of Transmission of Divine Power. Early pharmacopias spoke of iron as Mars Tincture of Syrup of Mars with Tartar.

The therapeutic use of iron is clinically linked with chlorosis in which it produced prompt and dramatic results. Although there may have been a reference to chlorosis in the writings of Hippocrates and other writers, credit for the first description of the disease goes to Jonannes Lange (1485-1565). To Thomas Sydenham (1624-1689) the great English Clinician must go the credit of popularising the use of iron which he advocated; chlorosis he labelled as a truly hysterial complaint. He advocated the simplest form of iron in the form of steel, preferably in a syrupy solution. He made this by steeping iron or steel filings in cold wine and when the wine was sufficiently impregnated with iron to stain the liquor, he added sugar to it and boiled it to the consistency of syrup. In 1836 Ashwell published a paper on chlorosis and its complications advocating iron in the form of ferrous carbonate and iodide of iron in large doses. Observations that depth of colour of blood in patients with chlorosis was lighter than normal was made by Hoefer in 1840 and five years later by Popp who found that the R. B. Cs. were paler in colour. It was Blaud who recognised that the condition arose from the faulty formation of blood and that iron restored the blood to normal. In the first edition of Osler's text book in 1891, the use of Blaud's pill for this condition has been advocated. Immermann in 1877 achieved great success with use of iron. Meulengracht in 1923 brought attention to the use of large doses of iron.

---

†Paper read at the Conference of the Association of Physicians of India, at Amritsar, in March 1951.

*Professor of Clinical Medicine, Medical College, Amritsar.

There remained a large number of cases who either could not tolerate iron by mouth properly due to indigestion, anorexia, troublesome diarrhoea or were suffering from bowel conditions such as diarrhoeas, dysenteries etc. which would be aggravated by iron. To meet these difficulties, the question of parenteral use of iron was considered.

Heath (1932), Goodman and Gilman (1941), Best and Taylor (1943) have shown that iron administered parenterally gave rise to toxic effects from precipitation of iron in the blood producing multiple pulmonary and sometimes systemic emboli with symptoms resembling those of fat embolism causing gastro-intestinal irritation and depression of the central nervous system leading to coma and death. Heath used iron ammonium citrate 32 mg. daily for about 10 days intramuscularly in 15 patients with hypochromic anaemia and this led to prohibitive toxic reactions although 96 per cent of it was utilised in the formation of haemoglobin.

The first successful attempt with saccharated iron oxide intravenously was made by Cappell in 1930 and he stated that this preparation was better tolerated than colloidal ferric oxide.

Goetsch *et al* (1946) gave colloidal iron hydroxide intravenously with alarming toxic results.

Nissim[6] in 1947 had the same experience but found that saccharated iron oxide gave very mild reactions.

Slack, Manc and Wilkinson[8] in 1949 used Benger's saccharated oxide of iron named Ferrivenin in 40 cases and an iron sucrose preparation of pH 10.5 in 20 cases. They agreed with Cappell and Nissim that saccharated oxide of iron was better tolerated without harmful effects and the utilisation of the intravenous sucrose preparation appeared to be 100 per cent. They also mentioned that 100 mg. of iron given intravenously should raise the haemoglobin by 0.55 Gm. per 100 cc. or 4 per cent on the Haldane scale.

Govan and Scott,[4] Sinclair and Duthie,[7] Cohen,[2] Mitchell[5] and French[3] in 1949 confirmed the efficacy and low toxicity of Ferrivenin.

It was also brought out that iron deficiency anaemias which were refractory to oral iron responded to intravenous iron.

In addition to intolerance of oral administration there is in this route, always, a slow response which is very time consuming, not only robbing man of working days which would naturally adversely affect the nation's wealth but also prolonging the stay in hospitals of such anaemia patients and thus enhancing the cost of the treatment.

INDICATIONS

The indications for intravenous iron depend on:—

1. The need for quick response in extremely anaemic cases.
2. Intolerance to oral use of iron.
3. Cases refractory to oral administration of iron.
4. Cost.

It is with this object of cutting down the hospital cost, of minimising the period of convalescence and accelerating the restoration of the earning capacity of these patients that we undertook the use of Ferrivenin intravenously. Ferrivenin is Benger's preparation of saccharated oxide of iron.

We are presenting nine cases of proved iron deficiency anaemias, microcytic hypochromic in type, and in every case complete weekly haemogram showing Haemoglobin, R. B. C., M. C. V., M. C. H. C., E. S. R., T. L. C., D. L. C., Total Proteins, Bilirubin, Reticulocyte count and Blood Iron was done throughout the course of treatment. The causes of anaemias in these cases have been ancylostomiasis, malaria and piles. All these investigatons and administration of iron intravenously was carried out by Dr. Kailal Chand Pasi in my department. The haemogram of each case is reproduced in tabular form (pages 438-42). The response to iron is shown in graphic from (pages 443-47).

RESULTS

Response has been dramatic. Dyspeptic symptoms improved, appetite was quickly restored to normal, weakness, dyspnoea, tiredness and palpitation disappeared with good speed. A sense of well being was noticed early during the course of treatment. In the first two weeks Haemoglobin had risen from 0.9 Gm. to 4.9 Gm. except in one case of a malignant growth of the stomach, and red blood cells from 0 million to 1.8 million: during the succeeding two weeks haemoglobin had risen from 0.3 Gm. to 3.6 Gm. and red blood cells from 0.1 million to 0.9 million. M. C. V. and M. C. H. C. gradually increased and E. S. R. gradually dropped to normal limits at a progressive rate. Treatment was given for 25 days when

TABLE I.—*Showing Complete Weekly Haemogram.*

Date	Hb	RBC	PCV	MCV	MCH	MCHC	ESR	Leucocytes						Abnormal cell Proteins	Bilirubin	Reticulocyte count	Remarks Iron
								Total	N	L	M	E	B				
23-6-50	3.5	2.4	18	75	14.6	19.4	63	8000	65	26	1	8	—	6.52	Negligible	0.5	12.8
30-6-50	5.0	2.8	21.3	76.07	17.8	23.4	43	8400	61	28	2	8	—	6.7	,,	9.8	16.8
7-7-50	8.0	4.2	32	76.19	19.1	25	24	8200	60	31	1	8	—	6.7	,,	2.8	27.1
14-7-50	9.4	4.3	35	81.39	21.86	27	27	7850	62	30	—	8	—	6.7	,,	0.5	32.0
21-7-50	10.1	4.5	37.2	82.6	22.4	27.1	24	8050	61	30	1	8	—	6.85	,,	0.45	33.7
28-7-50	11.1	4.8	40.8	85	23.1	27.2	21	8100	63	27	1	9	—	6.85	,,	0.51	37.2
4-8-50	12.3	4.8	41	85.4	25.5	30	20	8150	63	27	1	9	—	6.85	,,	0.5	41.1
11-8-50	12.4	4.8	41	85.4	25.8	30.2	20	8000	64	30	2	4	—	6.85	,,	0.49	44.6
8-9-50	15.7	5.2	45	86.53	30.19	34	10	7200	63	32	1	4	—	6.85	,,	0.8	53.7
19-10-50	15.7	5.3	45.4	85.66	29.62	34.58	10	7500	62	33	3	1.5	0.5	6.85	,,	0.71	54.0
21-11-50	15.7	5.3	45.4	85.66	29.62	34.58	8	7350	63	32	3	2	—	6.85	,,	0.48	54.0

TABLE 2.—*Showing Complete Weekly Haemogram.*

Date	Hb	RBC	PCV	MCV	MCH	MCHC	ESR	Leucocytes						Abnormal cell Proteins	Bilirubin	Reticulocyte count	Remarks Iron
								Total	N	L	M	E	B				
26-6-50	3.75	2.3	14	60.8	16.3	26.7	78	8000	70	23	2	5	—	6.85	Negligible	1.0	13.5
2-7-50	6.75	2.9	23	79.3	23.2	29.3	57	8200	68	25	1	6	—	6.85	,,	11.5	—
9-7-50	10.1	3.9	32.5	83.3	25.8	31.07	56	8100	65	29	1	5	—	6.85	,,	5.1	33.1
16-7-50	10.4	3.98	33.3	83.66	26.13	31.23	54	8200	63	29	1	6.5	0.5	6.85	,,	0.9	34.7
23-7-50	11.6	4.2	36	85.6	27.6	32.2	51	7900	61	30	1	8	—	6.85	,,	0.85	39
30-7-50.	12.8	4.3	37.5	87.2	29.7	24.1	48	8050	61	30.5	2	6	0.5	6.85	,	1.1	42.8

TABLE 3.—*Showing Complete Weekly Haemogram.*

Date	Hb	RBC	PCV	MCV	MCH	MCHC	ESR	Leucocytes						Abnormal cell Proteins	Bilirubin	Reticulocyte count	Remarks Iron
								Total	N	L	M	E	B				
30-8-50	2.5	1.54	10.5	68.18	15.12	23.8	65	7200	62	32	1.5	4	0.5	6.52	Negligible	0.8	9.25
8-9-50	5.6	2.5	21	84	22.4	26.66	48	7000	62	31	2	5	—	6.52	,,	8.7	19
15.9.50	8.4	3.5	30	85.61	24	28	27	7000	61	31.5	3.5	4	—	6.52	,,	0.85	28.75
22-9-50	10.7	3.9	34	87.17	27.43	31.47	17	6900	60	34	3	3	—	6.52	,,	0.8	36
29-9-50	12.6	4.6	40.5	88.04	27.39	31.11	16	6900	60	31	3	5.5	0.5	6.52	,,	0.9	42
9-10-50	14.2	4.6	43	93.47	30.86	33.02	2	6800	62.5	31.5	1.5	4	0.5	6.52	,,	0.62	47.5

TABLE 4.—*Showing Complete Weekly Haemogram.*

Date	Hb	RBC	PCV	MCV	MCH	MCHC	ESR	Leucocytes						Abnormal cell Proteins	Bilirubin	Reticulocyte count	Remarks Iron
								Total	N	L	M	E	B				
4-9-50	5.8	3.7	24	64.8	15.6	24.1	39	6900	61	32	2	5	—	5.031	Negligible	0.85	19.5
11-9-50	7.8	4.2	31	73.80	18.57	25.16	44	6750	62	32.5	1	4.5	—		,,	3.1	26.25
18-9-50	7.8	4.0	29	72.5	19.5	26.2	26	7000	60	33.5	2	4	0.5		,,	0.85	27.0
25-9-50	10.4	4.9	36	73.46	21.22	28.88	9	7100	60	31	3	6	—		,,	0.79	35
2-10-50	11.6	5.2	39	75.0	22.19	29.74	11	7050	61	30.5	3.5	4.5	0.5		,,	0.73	—
9-10-50	12.1	5.1	39	76.47	23.72	31.02	5	7000	62	30.5	3.5	4	—		,,	0.7	40
16-10-50	12.7	5.1	39	76.47	24.90	32.56	3	7200	60	35	2	2.5	0.5		,,	0.7	—
23-10-50	13.0	5.15	40	77.66	25.24	32.5	5	6900	59	33	3	4.5	0.5		,,	0.7	43
30-10-50	13.7	5.2	41	78.84	26.34	33.41	7	6950	59.5	32.5	3.5	4	0.5		,,	0.65	45.5

TABLE 5.—*Showing Complete Weekly Haemogram.*

Date	Hb	REC	PCV	MCV	MCH	MCHC	ESR	Leucocytes						Abnormal cell Proteins	Bilirubin	Reticulocyte count	Remarks Iron
								Total	N	L	M	E	B				
10-9-50	2.9	2.0	12	60	14.5	23.16	77	6900	61.5	30	2	6.5	—	6.52	Negligible	0.43	9.75
18-9-50	7.8	3.4	25.5	75	22.94	30.58	34	6850	60	30	4.5	5	0.5	6.52	,,	11.5	26.25
24-9-50	11.6	4.4	38	86.36	26.36	30.52	34	6900	62	29	3	6	0.5	6.52	,,	1.6	37.5
1-10 50	12.4	4.5	38.9	86.44	27.55	31.87	33	7000	62	30	3	7	—	6.52	,,	0.82	40.0

TABLE 6.—*Showing Complete Weekly Haemogram.*

Date	Hb	RBC	PCV	MCV	MCH	MCHC	ESR	Leucocytes						Abnormal cell Proteins	Bilirubin	Reticulocyte count	Remarks Iron
								Total	N	L	M	E	B				
3-10-50	3.2	2.04	15	73.52	15.62	21.33	70	7500	65	27	2	6	—	6.52	Negligible	0.59	10.5
11-10-50	7.5	3.8	33	86.84	19.73	22.72	43	7200	64	27	2	6.5	0.5	6.52	,,	10.9	25
18-10-50	9.1	3.8	33	86.84	23.94	27.54	40	7300	65	26	2	6.5	0.5	6.85	,,	0.9	30.4
25-10-50	12.7	4.3	38	88.37	29.53	33.42	28	7100	66	27	1	6	—	6.85	,,	0.63	42
1-11-50	13.4	4.5	40	88.88	29.77	33.5	27	7000	66	26.5	1	6.5	—	6.85	,,	0.54	44.5
8-11-50	14.5	4.7	43	91.48	30.85	33.72	15	6900	65.5	27	1	6	0.5	6.85	,,	0.6	48
17-11-50	14.9	4.8	44	91.66	31.04	33.86	4	6900	66	27.5	1.5	5	—	6.85	,,	0.61	49.5

TABLE 7.—*Showing Complete Weekly Haemogram.*

Date	Hb	RBC	PCV	MCV	MCH	MCHC	ESR	Leucocytes						Abnormal cell Proteins	Bilirubin	Reticulocyte count	Remarks Iron
								Total	N	L	M	E	B				
5-10-50	3.1	2.0	14	70	15.5	22.14	73	8850	67	25	1	7	—	6.52	Negligible	0.5	10.5
13-10-50	7.5	3.5	29	82.85	21.42	25.86	60	8650	65	26	1	7.5	0.5	6.52	,,	9.8	25.2
20-10-50	9.1	3.5	31	88.57	26.0	29.35	46	8000	63	28.5	1	7	0.5	6.52	,,	1.6	31
27-10-50	11.2	3.8	34.5	90.78	29.47	32.46	54	8000	63	28	1	8	—	6.52	,,	0.87	37.5
3-11-50	11.6	4.05	37	91.35	28.62	31.34	54	7900	62	29	1	7.5	0.5	6.52	,,	0.6	39
10-11-50	12.9	4.3	40	93.02	30	32.25	45	7800	62	29	1.5	7.5	—	6.52	,,	0.59	43.5

TABLE 8.—*Showing Complete Weekly Haemogram.*

Date	Hb	RBC	PCV	MCV	MCH	MCHC	ESR	Leucocytes						Abnormal cell Proteins	Bilirubin	Reticulocyte count	Remarks Iron
								Total	N	L	M	E	B				
30-10-50	4.6	3.0	19	63.33	15.33	24.71	60	6950	65	28	3	4		6.52	Negligible	0.49	15
8-11-50	8.2	3.9	31	79.48	21.02	26.45	40	7000	66	28	2	4	—	6.52	,,	11.9	27.5
15-11-50	11	4.2	35.5	84.52	26.19	30.98	24	7100	65.5	27.5	2	4.5	0.5	6.52	,,	0.65	36.5
23-11-50	14.2	4.7	41.5	88.29	30.21	34.31	17	6950	63.5	30.5	2	4	—	6.52	,,	0.6	47.5

TABLE 9.—*Showing Complete Weekly Haemogram.*

Date	Hb	RBC	PCV	MCV	MCH	MCHC	ESR	Leucocytes						Abnormal cell Proteins	Bilirubin	Reticulocyte count	Remarks Iron
								Total	N	L	M	E	B				
30-10-50	5.3	3.14	22	73.24	16.87	24.09	60	6000	66	26	1	7	—	6.52	Negligible	0.6	17.6
6-11-50	8.9	3.7	29.4	79.45	24.05	30.27	35	6200	66	26	0.5	7	0.5	,,	,,	10.1	29.5
13-11-50	9.8	3.9	32	82.05	25.12	30.62	30	6100	66	27	1	6	—	,,	,,	1.1	32.5
20-11-50	11.4	4.2	37	88.09	27.14	30.81	16	6000	65	27	1.5	6	0.5	,,	,,	0.67	38
18-1-51	15	4.5	44	97-77	33.33	34.09	4	6100	66	26	1.5	6	0.5	,,	,,	0.61	49.5

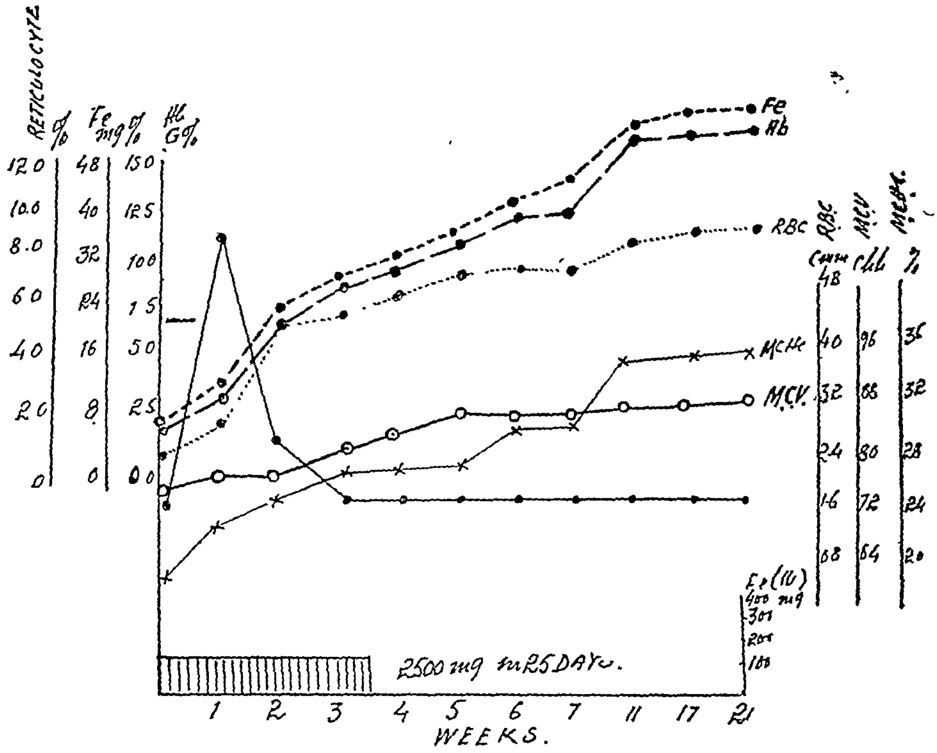


Fig. 1.—Graph showing response to iron.

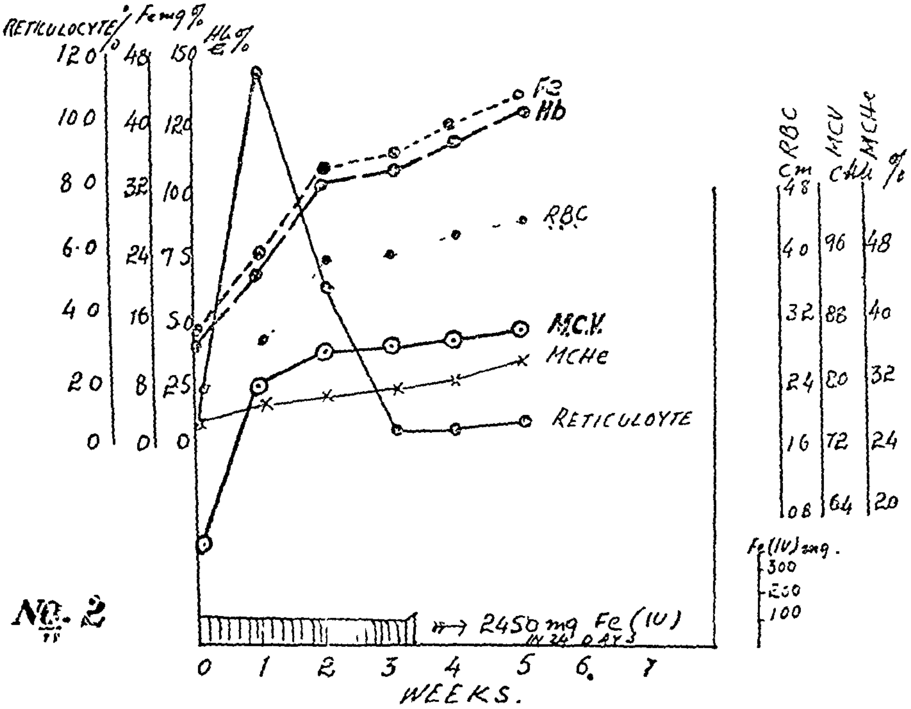


Fig. 2.—Graph showing response to iron.

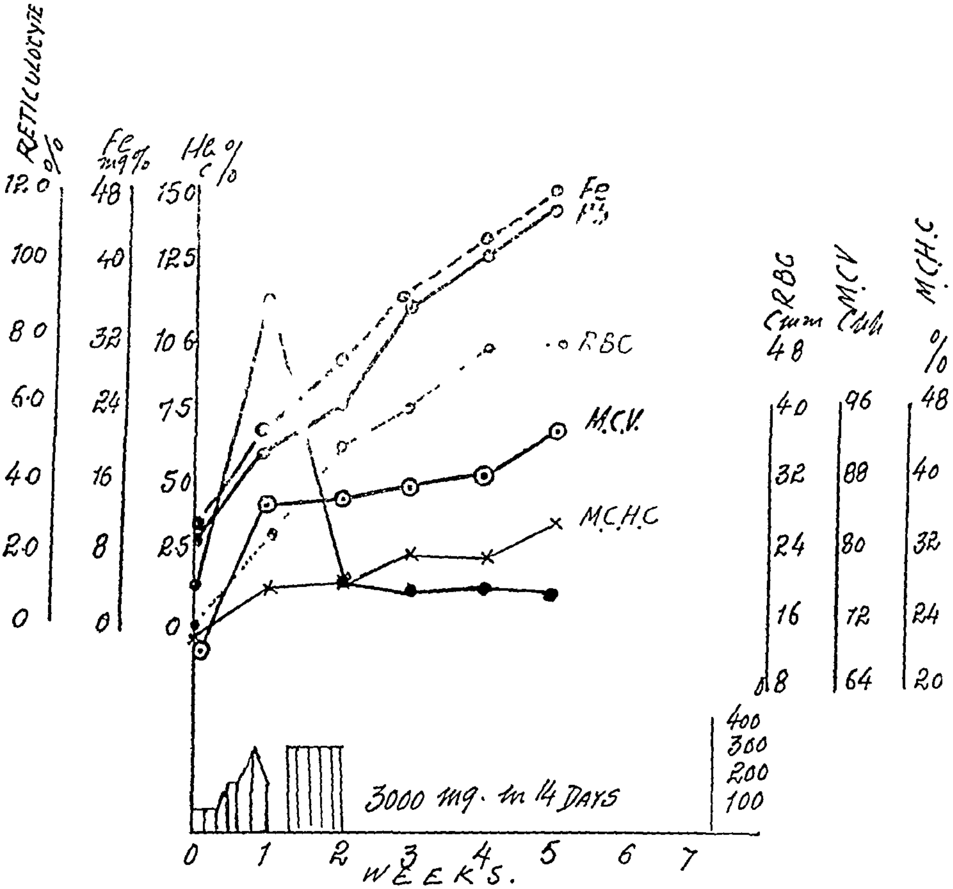


Fig. 2.—Graph showing response to iron.

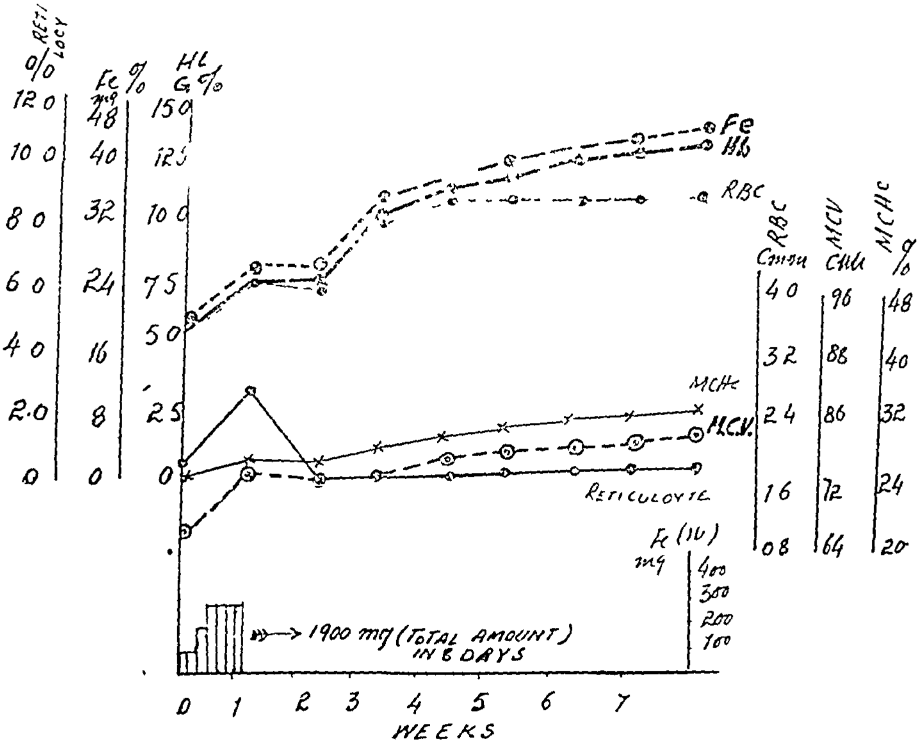


Fig. 4.—Malignant Stomach. Graph showing response to iron.

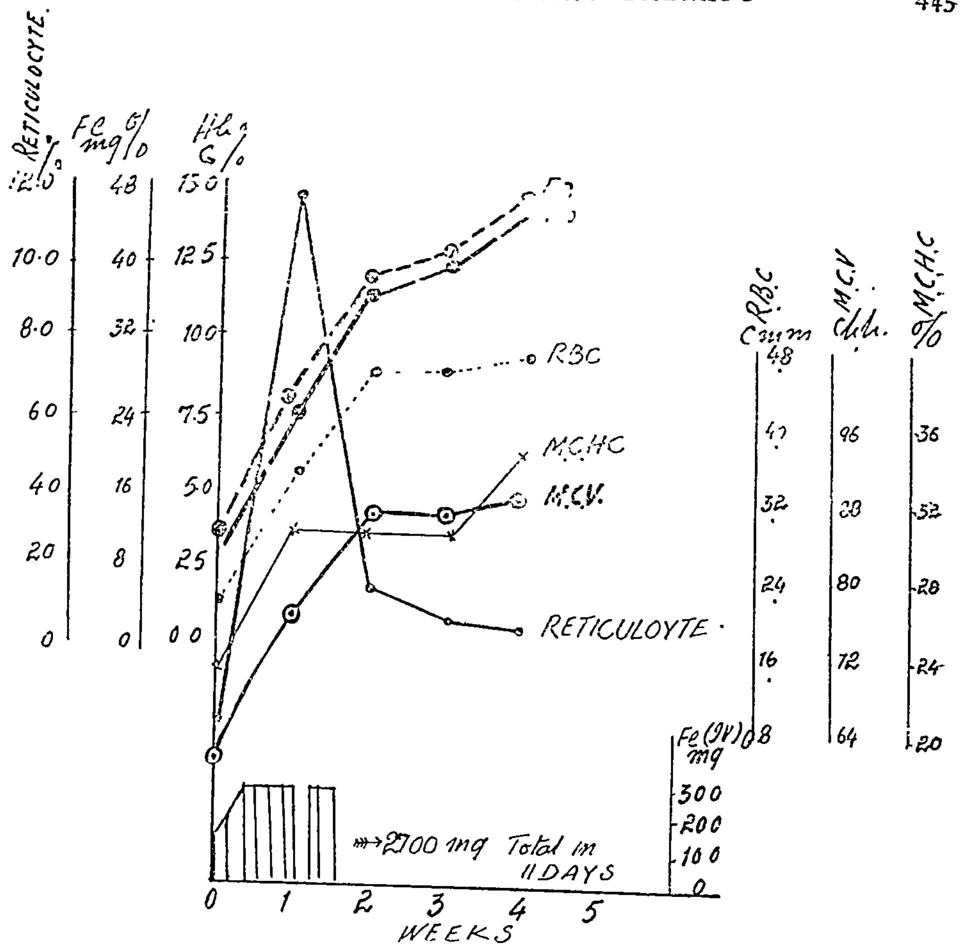


Fig. 5.—Graph showing response to iron.

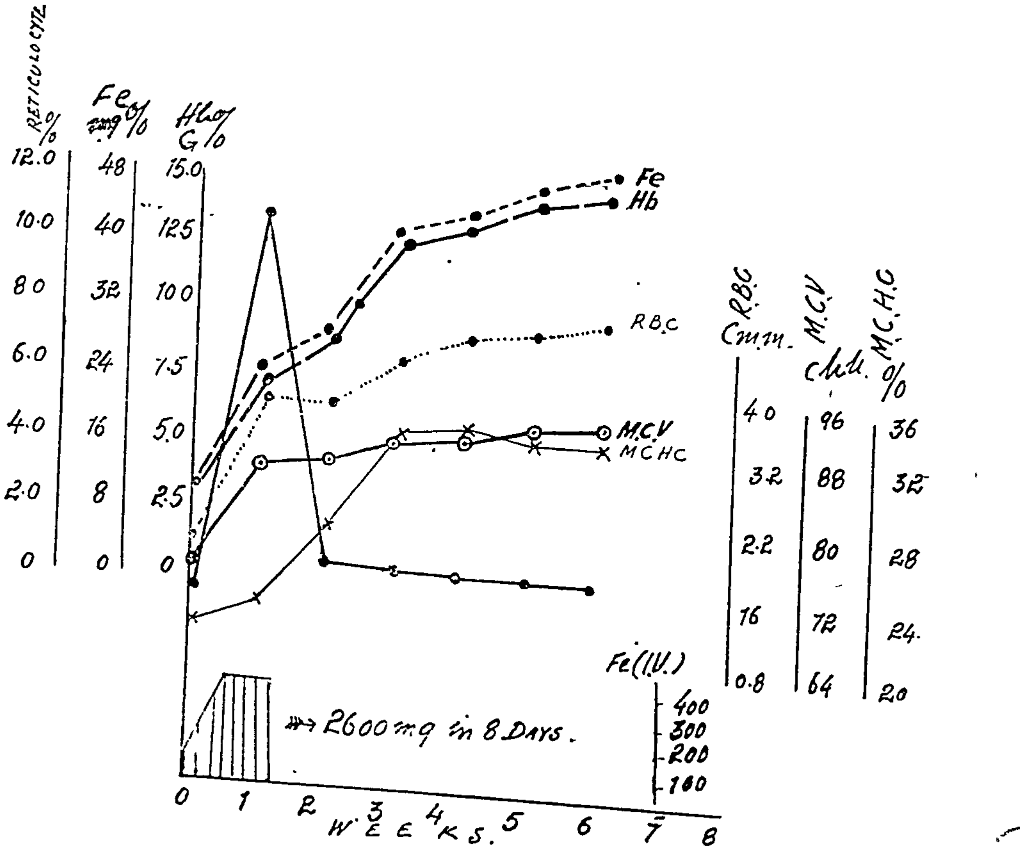


Fig. 6.—Graph showing response to iron.

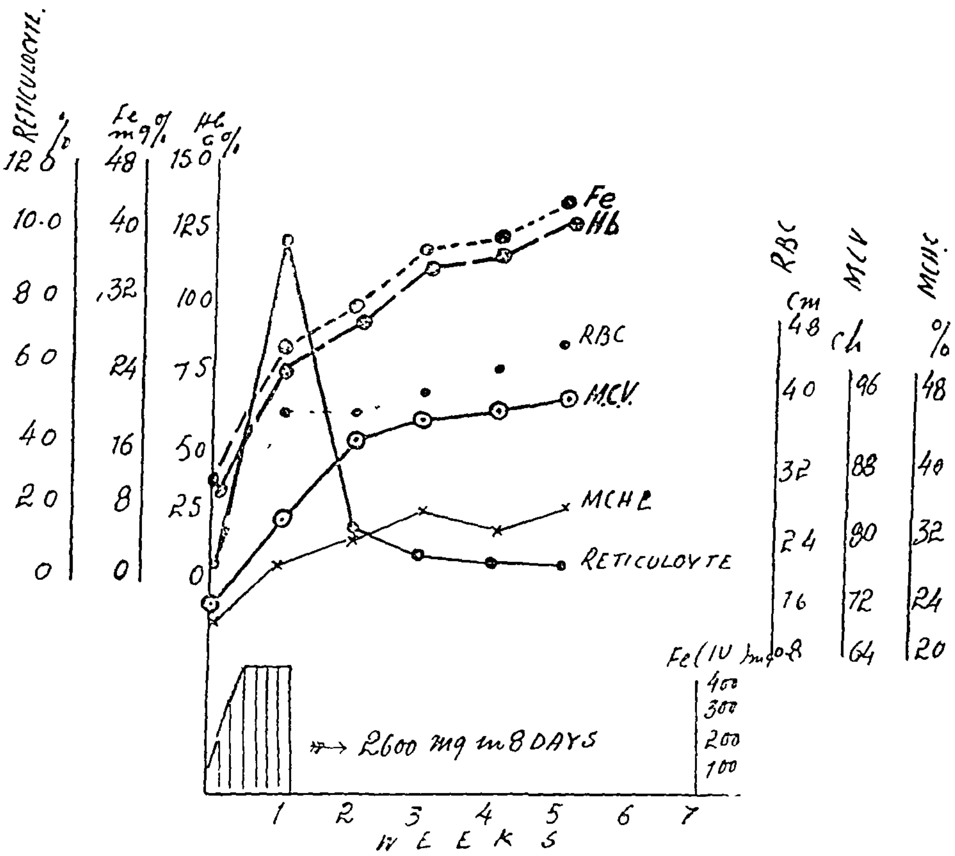


Fig. 7.—Graph showing response to iron.

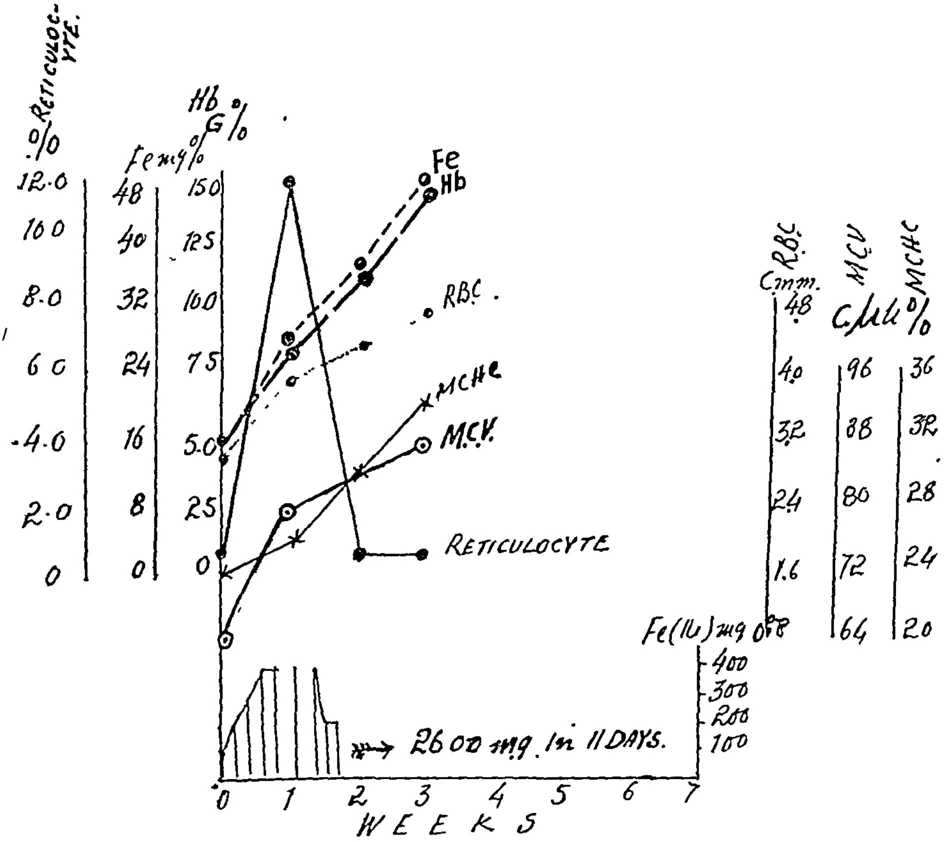


Fig. 8.—Graph showing response to iron.

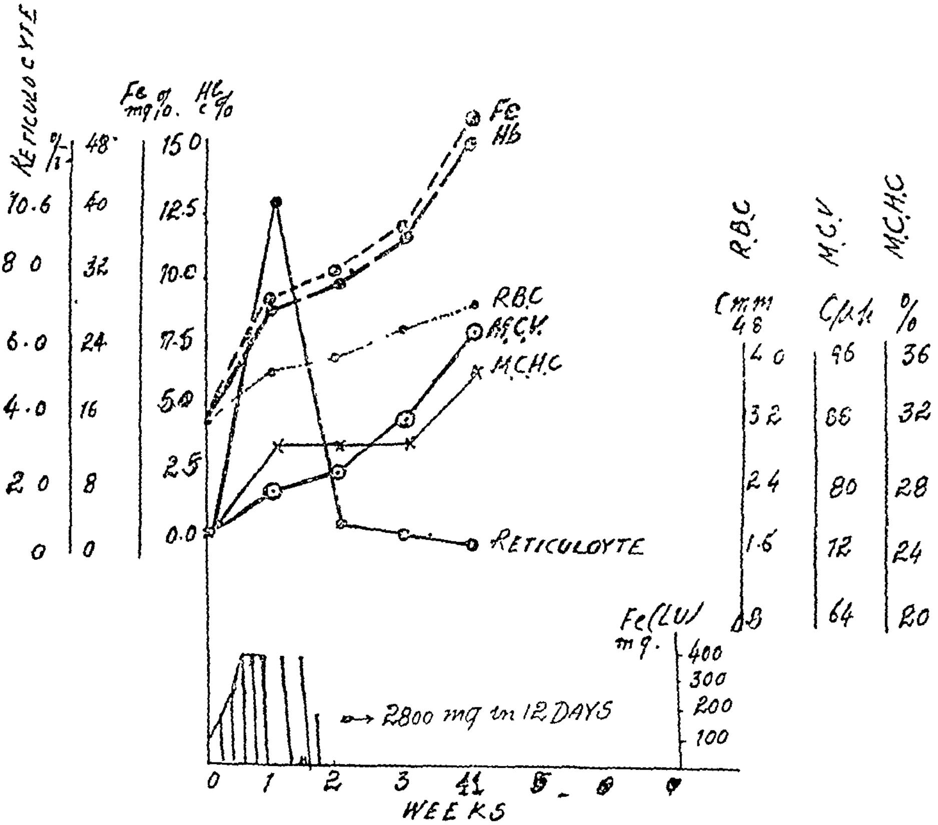


Fig. 9.—Graph showing response to iron.

100 mg. was given daily and for about 8 days when 400 mg. was given daily.

DISCUSSION

Although the ideal is to give the calculated deficit of iron plus another 50 per cent for iron storage which is in a depleted condition in anaemias' but due to the paucity of funds which were met from a private source by Dr. K. C. Pasi and the limited supply, only the calculated deficit of iron was given intravenously.

The stay of patients in the hospital for the treatment of anaemia has been 25 days when 100 mg. was given daily and 8 days when 400 mg. was given daily, which is a no mean achievement considering that some patients had as low as 2.5 Gm of Haemoglobin and 1.5 million R. B. Cs. and their digestive system was in a very impoverished state not being able to digest even liquid diet. In some cases the chances of cure by any other means would have been negligible because for controlling the diarrhoea, the diet had to be cut down thereby reducing Haemoglobin and R. B. Cs. to a still lower level.

Again in this part of the country, the arrangements for blood transfusions are not easily available at all places and to all types of patients, without which the survival of such patients is difficult to conceive, and it would be apparent from the results that intravenous iron can be administered in the most remote country home and environments if only sterilization of syringes and some patience in giving the intravenous injection slowly is exercised. The average cost of 100 mg. of elemental iron is about Rs. 2|- and for 25 injections it means Rs. 50|-. This would be much cheaper compared to the cost of blood transfusion, oral administration of iron and the nourishing diet and prolonged period of inability to earn.

SUMMARY

1. Nine cases of proved iron deficiency anaemia, microcytic hypochromic in type have been treated with Ferrivenin intravenously.

2. Doses varying from 100 mg. per day to 400 mg. daily have been given without any toxic or untoward reaction.

3. The value of intravenous iron in quickly restoring the haemoglobin and red blood cells to normal level and return him to earning capacity has been brought out.

4. The blood condition steadily improved after the calculated deficit of iron had been administered.

5. Compared to other methods of treatment of this type of anaemia, intravenous iron therapy appears to be the cheapest.

REFERENCES:

1. Cohen H., Advances in Medicine, Practitioner; 161: 233-246, 1948.
2. French D. G.: Intravenous Treatment of Anaemia with an Iron Sucrose Preparation. Lancet 1: 370, 1949.
3. Govan, A. D. T. and Scott, J. M.: Intravenous Iron in Treatment of Anaemia of Pregnancy, Lancet 1: 14-16, 1949.
4. Mitchell, D.: (1949) J. Med. Ass. Eire 24-25.
5. Nissim, J. A.: Intravenous Administration of Iron, Lancet, 2: 49-51, 1947.
6. Sinclair, H. G. B. and Duthie, J. F.: Intravenous Iron in Hypochromic Anaemia Associated with Rheumatoid Arthritis, Lancet, 2: 646-648, 1949.
7. Slack, H. G. B., and Wilkinson, J. F.: Intravenous Treatment of Anaemia with an Iron Sucrose Preparation, Lancet, 1: 11-14, 1949.
8. Strugis, C. G.: Diagnosis & Treatment of Anaemias, Post-graduate Medicine 3: 441-448, 1148.

INTRAVENOUS IRON IN THE TREATMENT OF ANÆMIA

G. K. Dhariwal & G. P. Mehta*

It is not uncommon to see patients suffering from iron-deficiency anaemia. The milder forms are frequently treated in the out-patient department with oral iron therapy but those suffering from a severe degree of anaemia are admitted to the hospital.

The demand for admission to the hospital is great but owing to the shortage of bed accomodation only a limited number of patients can be admitted. In this series, pregnant patients with anaemia are included.

The following is a review of 18 cases of hypochromic anaemia treated with intravenous iron in the medical unit of the Lady Hardinge Medical College and Hospital from September 1950 to April 1951.

The indications for this mode of therapy were as follows:

(1) Inability to tolerate iron by mouth.

(2) Diarrhoea, dysentery or vomiting.

(3) Where blood transfusion was not available.

(4) To reduce the period of hospitalisation.

This series consists of cases mostly from the poor with the exception of three who were of middle class families. Most of them had foods deficient in iron, others suffered from ankylostomiasis, malaria, epistaxis, irregular and profuse uterine bleeding, dysentery or diarrhoea.

TECHNIQUE OF ADMINISTRATION

Injection technique: Iron was given intravenously using 5 or 10 cc. record syringe with number 12 needle through the antecubital veins or the veins of the dorsum of the hands if the former were not available. The same vein was not used on consecutive days in the same case. The time taken for giving the injection was from 1—2½ minutes for 5 cc. No follow-on lavage of the vein was done in any case. Leakage of the solution in the surrounding tissues resulted in pain and swelling of the affected limbs.

Dosage: The first dose used was a test dose of 40 mg. and the successive ones were 100 mg. each in 5 cc. In the majority of cases the total number of injections given were 6—12 either daily or on alternate days.

---

*From the Department of Medicine, Lady Hardinge Medical College, New Delhi.

Reactions: With the dosage described above very mild reactions were observed. In some cases there was a slight fall in the blood pressure. Some patients complained of dyspnoea, pain in the chest, back and abdomen. These symptoms lasted for a few minutes with the exception of pain in the chest which lasted for a few hours. One patient became unconscious on slight exertion immediately after the injection. We did not encounter any rigors or pyrexia following intravenous iron therapy. On the contrary some of our cases of mild pyrexia became apyrexial as their anaemia improved.

Preparations of intravenous iron: Those used by us were "Iviron" manufactured by British Schering Limited, London and "Uniferon,, prepared by Unichem Laboratories, Bombay. There has been no appreciable difference in tolerance or response to either of these two preparations. The latter is cheaper and so within easy reach of a middle class patient.

Response to treatment: These saccharated iron oxide preparations are safe and effective when administered intravenously. Our patients improved markedly regarding the appetite, general weakness, dyspnoea and palpitation. Their oedema disappeared and they looked cheerful. In those cases where anaemia was severe with loud haemic murmurs and enlargement of the heart, the condition became normal as anaemia responded to treatment. In some of our cases enlargement of the liver and spleen was present to about two to three fingers breadth below the costal margin. The former became smaller as anaemia improved but no appreciable change was noticed in the size of the spleen.

DISCUSSION

Table 1 shows the effect of intravenous iron on 18 cases of hypochromic and one of normochromic anaemia, with good response in the majority of cases, failure in case number 2, and poor response in case numbers 5 and 14.

The table shows haemoglobin levels before and after intravenous iron therapy. All these patients were on the same regime which included light or full diet, vitamins and extra proteins if necessary.

Sternal marrow biopsies were performed in 7 cases and all showed normal active marrow.

Gastric analysis was done in 12 cases. Of these, 7 were within normal limits, 3 showed hypochlorhydria and 2 had histamine fast achlorhydria. Incidentally the last two did not show good results. Cases in which poor response was obtained were those where pyrexia and some infection were present. Slack and Wilkinson[6] (1949) ob-

TABLE I.—*Showing Results of Haematological Investigation on 19 Cases before and after Treatment with Intravenous Iron Administration.*

BEFORE TREATMENT.															AFTER TREATMENT					
No.	Age	Sex	Diet	Gravida	Gastric acidity	Hgb. % Sahli	Hgb. Gm% per 100 cc.	RBC in millions	MCV Cum	MCH γγ	MCHC %	Plasma protein Gms/100 cc.	Days	Total in mg.	Hgb. % Sahli	Hgb. Gms.% per 100 cc.	RBC in millions	MCV Cum	MCH γγ	MCHC%
1	30	F	Mixed	9th.	Normal	30	5	2	80	25	30	4.2	11	900	50	8.5	3	93	28	30
2	20	F	Mixed	2nd	H-fast achlorhydria	30	5	3	70	17	23	5.1	8	700	36	6.1	2.56	99	24	26
3	30	F	Veg.	—	Normal	30	5.1	2.95	65	17.2	26	5.08	—	1200	54	9.1	3.1	—	—	—
4	17	F	Mixed	—	Normal	24	4.08	2.8	64	15	22	5.7	7	700	64	11.0	4.1	95	27	28
5	7/12	MC	Milk	—	—	30	5.00	2.8	80	21	23	—	4	300	40	—	3	—	—	—
6	26	F	Veg.	—	Low	30	5	3.96	73	17	23	7.8	6	600	68	11.65	4.1	95	29	30
7	40	F	Mixed	—	—	18	3	1.8	89	19	19	—	6	600	60	10.2	3.65	93	28	30
8	27	F	Mixed	—	—	46	8	3.6	94	22	20	—	9	900	68	11.65	4.23	94	27	29
9	8	FC	Mixed	—	—	16	2.7	2.4	62.5	11.3	18	5	13	600	78	13.26	4.5	95	29	30
10	11	F	Mixed	—	Low	10	1.7	1.4	50	12	24	3.9	18	800	70	12	4.1	83	30	35
11	14	F	Mixed	—	Normal	20	3.4	2.4	70	15	20	—	12	1000	70	11.9	4.1	90	29	32
12	22	F	Mixed	3rd	Normal	44	7.4	3.52	86	21	24	5.3	20	800	72	12.24	4.1	80	29	36
13	24	F	Mixed	—	Normal	30	5	2	75	25	33	5.4	22	1100	80	13.5	4.55	92	32	32
14	30	F	Veg.	—	H-fast achlorhydria	14	2.38	2	70	11.9	17	3.5	20	1100	38	6.4	2.7	111	24	26
15	8	MC	Mixed	—	—	Below 10	—	1.2	67	—	—	4.9	12	1200	40	6.8	3.7	—	—	—
16	26	F	Veg.	—	—	34	5.78	3	73	19	26	—	8	750	54	9.18	4	80	22.9	28
17	10	MC	Veg.	—	—	34	5.78	3.6	77	16	20	7	7	700	80	13.6	5	72	27	37
18	44	F	Veg.	—	Normal	48	8	3.6	94	22	23	—	5	450	58	10	4.07	93	24.5	27
19	20	F	Mixed	—	Low	26	4.54	2.39	100	19	19	—	9	900	50	8	3.9	100	21	22

served that in chronic infection there is a greatly increased demand for iron by the cell systems of the body and that very large amounts of iron must be provided to enable the bone marrow to obtain sufficient iron for its purposes and to maintain a normal plasma-iron level.

Case number 8 was treated with iron by mouth for 16 days and the response was very slow (an increase of 6 per cent Sahli) compared to intravenous therapy which was started later, and within 7 days after a total of 700 mg., the haemoglobin rise was 22 per cent (Sahli). The same fact holds good in case number 3.

Utilisation of intravenous iron preparation appears to be nearly 100 per cent and the loss by urinary excretion negligible.

One thing which we wish to point out is that the estimation of the haemoglobin and the R. B. C. count after treatment was done a day or two after the last injection in the majority of cases. Perhaps if we had taken another reading after a few days inspite of not giving any more iron by mouth or parenterally, a further rise in haemoglobin levels may have been observed.

In our series the average rise in haemoglobin after 100 mg. of intravenous injection was 4.2 per cent.

SUMMARY.

Intravenous iron is a safe and effective method of treating hypochromic anaemia when iron by mouth is not tolerated and when a quick response is desired.

As sufficient voluntary donors are not available for blood transfusion this form of therapy is of great help.

Preparation, dosage and injection technique are described in detail.

Toxic effects are avoided when a test dose is given first and increased later to 100 mg.

Our thanks are due to Col. Amir Chand for the encouragement and valuable suggestions, and to Dr. P. Malkani for her kind assistance.

REFERENCES

1. Davidson, L. S. P., and Girdwood, R. H.: Refractory Iron Deficiency Anaemia Treated with Intravenous Saccharated Iron Oxide, B.M.J. 1: 733-734, 1948.
2. Govan, A. D. T. and Scott, J. M.: Intravenous Iron in Anaemia of Pregnancy, Lancet 1: 14-16, 1949.
3. Nissim, J. A.: Intravenous Administration of Iron, Lancet 2: 49-51, 1947.

4. Robson, J. M. and Keele, C. A.: Recent Advances in Pharmacology, pp. 269-285, J. A. Churchill, London, 1950.
5. Sinclair, R. J. G.. and Duthie, J. J. R.: Intravenous Iron in Hypochromic Anaemia with Rheumatoid Arthritis, Lancet, 2: 646-648, 1949.
6. Slack, H. G. B. and Wilkinson, J. F.: Intravenous Treatment of Anaemia with Iron-Sucrose Preparation, Lancet 1: 11-14, 1949.
7. Whitby, Sir Lionel E. H. and Britton, C. J. C.: Disorders of the Blood. 5th Edition. J. A. Churchill, London 1947.
8. Ramsay, A. S.: Intravenous Iron in the Treatment of Anaemia, 1: 1109-1112, 1950.

SOME OBSERVATIONS ON ANÆMIA OF ANCYLOSTOMIASIS WITH SPECIAL REFERENCE TO IRON THERAPY †

Miss Sharma* & B. B. Bhatia.*

In recent years some doubts have been thrown on the role of Ancylostome duodenale in the causation of anaemia. Some authorities are of the opinion that only heavy and moderately severe infections are responsible for anaemia. If anaemia is present with mild infection then it is usually presumed to be due to some other contributory factors, such as nutritional deficiency, gastro-intestinal disturbances, chronic-malaria etc.

It was therefore felt, that in a country like India, where in some states in the rural areas, 30-40 per cent of the adult male population is infested with these worms and have considerably lowered vitality, that the medical science should be able to give a definite answer about the pathogenic role of these worms.

We should be able to say whether the mass eradication of ancylostomiasis is more urgent in the interest of national health, or the provision of more nutritional food.

The following observations have been made to throw some light on this question and they are being presented at this Conference of the Association of Physicians of India, so that similar observations may be made in other States and with the help of data thus collected a definite answer may be given, whether **Ancylostome duodenale** is an important cause of anaemia in this country or not.

During the last 20 years, 762 cases of ancylostomiasis were admitted in the medical wards of K. G. Hospital, Lucknow. Their age and sex is given in Table 1.

In Table 2 is given the type of anaemia in 135 cases in which absolute values of the blood were done. It is obvious from this table that in nearly 80% of the cases the anaemia is of an iron-deficiency type, but in the other 20% cases the anaemia is of the other forms. Whether this is due to the presence of some other contributory factor, or to a different response in different constitutions is again a question on which further observations are necessary. We have come across a few cases in which during the course of Iron therapy anaemia has changed its character from *Microcytic Hypochromic* to Macrocytic Hyperchromic.

---

†Paper read at the Conference of the Association of Physicians of India at Amritsar in March 1951.

*Department of Medicine, Lucknow University.

TABLE 1.—*Age & Sex Incidence in Ancylostomiasis* (762 *Cases Admitted in King George's Hospital.*)

Males	Females	Age in years	Frequency of cases	Percentage
686	76	1—5	Nil	
		5—10	20	2.6
		10—15	36	4.7
99.1%	9.9%	15—20	80	1.5
		20—25	119	15.6
		25—30	205	26.9
		30—35	118	15.5
		35—40	74	9.7
		40—45	50	6.6
		45—50	29	3.8
		50—55	13	1.7
		55—60	9	1.2
		60—65	7	0.94
		65—70	2	0.26
		70—75	Nil	
		75-Above	Nil	

In Table 3 is given the relationship between the number of worms expelled after treatment and the extent of anaemia. In these cases reasonable care was taken to exclude the presence of other contributory causes of anaemia. The worms expelled were carefully counted and it was presumed that all the worms were expelled because 3—4 subsequent stool examinations done at weekly intervals were negative for the presence of ova. It is obvious from the perusal of the table that there is no relationship between the number of worms expelled and the degree of anaemia. In some cases in which only few worms were expelled the anaemia was quite severe. On the contrary there are some examples, where large number of worms were expelled, but the anaemia was of a mild type. If such disparity is seen, even when large number of cases are observed it will have to be admitted, that mild infestation can be a cause of severe anaemia.

TABLE 2.—*Types of Anæmia According to Absolute Values* (135 *cases.*)

Types of Anæmia	Frequency of cases	Percentage
1. Microcytic hypochromic ..	78	57.8%
2. Normocytic hypochromic ..	30	22.3%
3. Normocytic normochromic ..	12	8.8%
4. Macrocytic hypochromic ..	7	5.2%
5. Macrocytic hyperchromic ..	8	5.9%

TABLE 3.—*Relationship between R.B.C. & Hb% & No. of Worms Expelled.*

	R.B.C. in millions	Hb%	No. of worms		R.B.C. in millions	Hb%	No. of worms
1	1.6	26%	20	27	0.71	6%	184
2	0.85	18%	58	28	1.2	13.5%	107
3	1.9	27.6%	33	29	2.8	41%	12
4	2.65	39%	40	30	2.57	48.5%	8
5	1.86	26%	86	31	1.1	12%	60
6	1.18	15%	110	32	1.5	25%	132
7	1.72	27.6%	100	33	2.0	28%	44
8	0.97	15%	30	34	2.0	28%	180
9	3.12	56%	105	35	1.34	20%	70
10	1.13	17%	32	36	4.85	90%	59
11	0.91	14%	30	37	1.92	28%	50
12	1.65	31%	41	38	2.64	39.5%	8
13	1.05	17.4%	120	39	1.36	20%	30
14	2.2	38.6%	65	40	2.76	30%	12
15	1.55	23.5%	11	41	1.5	16%	100
16	1.01	17.4%	4	42	1.01	18%	8
17	2.9	48%	20	43	1.57	24%	45
18	2.3	41%	14	44	1.5	15%	45
19	1.6	16%	65	45	2.0	28%	36
20	2.7	36%	78	46	1.9	25%	2
21	1.8	20%	15	47	2.34	38%	200
22	2.45	54%	33	48	2.82	34%	12
23	1.5	20%	52	49	4.06	55%	10
24	1.58	22.5%	62	50	4.6	60%	2
25	1.32	12.5%	60	51	2.88	57%	1
26	1.5	18%	56	52	3.26	60%	12

In Table 4 are given the fractional test meal values and the extent of anaemia, and the number of worms expelled which further shows that abnormalities in gastric secretion do not play any contributory role in those cases where anaemia was severe in the presence of few worms.

From this it would appear that the extent of anaemia is either due to the duration of the infestation or due to different virulence of the worms or to a more susceptible nature of the host. We arrived at this conclusion after having eliminated any other contributory causes. It was not possible to find out the duration of the infestation as no reliable history of ground itch or vesicles over the feet was available.

It was equally difficult to decide whether the individuals manifesting a severe type of anaemia in the presence of few worms had any peculiar constitution which predisposed them to anaemia. They however, did not show any abnormality in the gastric secretion which is one of the factors concerned in the absorption of Iron.

At this stage it was also not possible to say whether the toxic action of the worms differed.

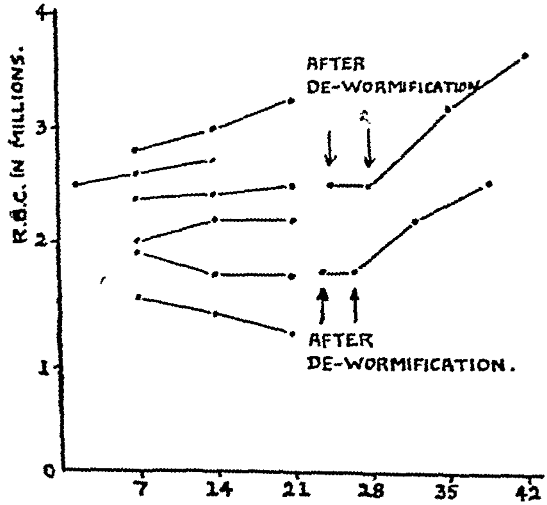
We further observed that iron therapy, parentral or oral, given

TABLE 4.—*Relationship Between Type of Gastric Curve, Anæmia and No. of Worms Expelled.*

Type of Gastric Analysis Curve	R.B.C. in millions		Hb%	No. of worms	No. of cases
Hyperchlorhydria	1	1.5	24%	45	7
	2	1.27	13.5%	107	
	3	1.8	20%	15	
	4	1.34	20%	70	
	5	1.36	24%	30	
	6	2.34	38%	68	
	7	2.7	36%		
Isochlorhydria	1	2.82	34%	12	9
	2	2.0	28%	190	
	3	1.5	20%	52	
	4	1.5	15%	100	
	5	1.5	15%	45	
	6	2.64	39.5%	8	
	7	1.6	16%	65	
	8	1.92	28%	50	
	9	1.01	18%	8	
Hypochlorhydria	1	1.5	25%	127	7
	2	1.5	18%	56	
	3	2.76	30%	12	
	4	0.71	6%	184	
	5	4.6	60%	2	
	6	2.45	54%	33	
	7	7.2	28%	36	

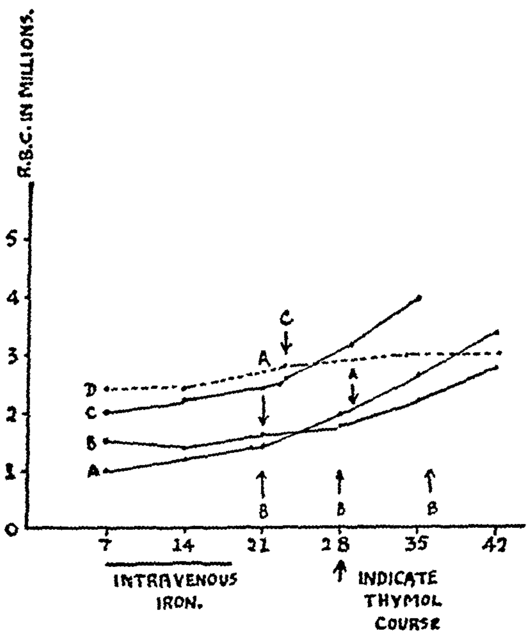
before dewormification was not very effective.

In Graph 1. are shown curves of six patients taken at random out of 34 cases, who were given oral iron—ferri et ammonium citras,



Graph 1.—Response to oral iron (60gr. of ferri-et-ammonium citras per day.)

grains thirty—twice a day for a period of 2 to 3 weeks along with a balanced diet, before dewormification. In 4 cases, there is slight increase in the number of RBC's and corresponding increase in haemoglobin percentage, but in the other two there is some fall in the number of RBC's; alongside are shown curves of 2 cases showing response to the same doses of oral iron after effective dewormification. Before dewormification, average increase of RBC's per cmm. in 15 days was 0.08 million per cmm. whereas after dewormification it was 0.9 million per cmm, nearly 10 times better response. Almost similar response was seen when iron was given by parentral route, iviron (Scherring) 5 cc. (equivalent to 100 mg.) daily for 10 days. In Graph 3. the average increase in the number of RBC's in 15 days before dewormification was 0.3 million per cmm. after dewormification and without further iron therapy the increase in RBC's was 1.1 million per cmm. It appears that the iron given by the parentral route was stored in the body and rapidly synthesised into haemoglobin once the worms were expelled.



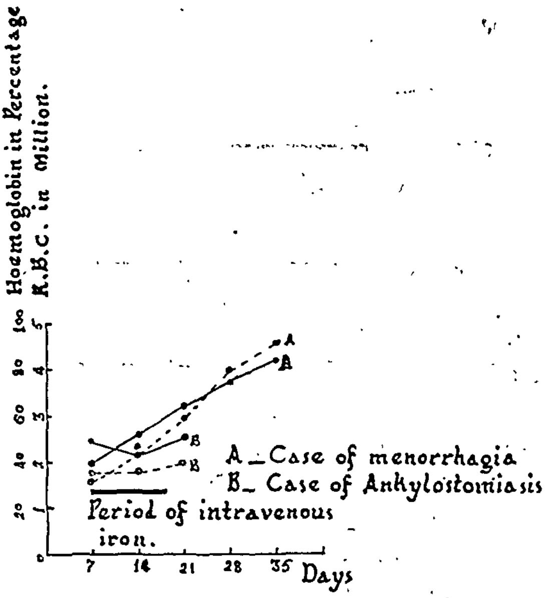
Graph 3 —Response of intravenous iron before de-wormification (curves A. B. C ;Curve D control).

It was quite obvious from these observations that these worms have got an important pathogenic role in the causation of anaemia and that dewormification in the beginning of the treatment is very necessary for effective iron therapy. In fact we feel that once dewormification has taken place, even the ordinary diet will be able to provide enough Iron to cure the anaemia and administration of Iron, by parentral or oral route will only help to hasten the period of recovery.

How these worms produce anaemia, is again a question which has not been satisfactorily answered. Some experimental evidence has been put forward to show that anaemia is due to small haemorrhages taking place from the mucous membrane where the worms had hooked themselves and then changed over to another site.

In large number of our cases we were not able to find any RBC's in the stool or the presence of occult blood by the chemical tests. In such cases it was therefore presumed that internal haemorrhages were not taking place.

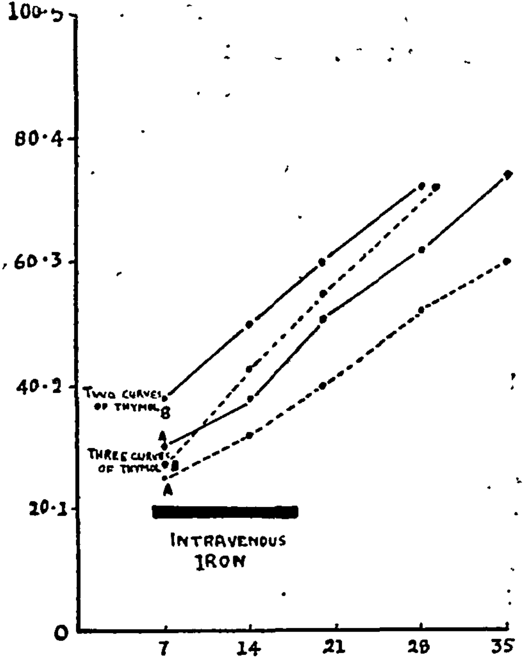
In Graph 2 is shown the response to parentral iron therapy in a case of severe anaemia due to recurrent menorrhagia and in a case of Ancylostomiasis. The response shown by the case of menorrhagia is very striking in comparison to that of Ancylostomiasis. If haemorrhage was the cause in both the cases, response should have been more or less similar. We therefore feel that haemorrhage is not an important cause of ancylostomiasis' anaemia. Some people feel that lack of absorption of iron is the cause of this anaemia. If that was so parentral iron therapy before dewormification would have been as effective as after dewormification. This however was not our experience.



Graph 2.—Response to intravenous iron in a case of menorrhagia and ancylostomiasis.

We are inclined to feel that these worms elaborate some toxic substance which prevents the synthesis of Iron into haemoglobin.

Graph 4. We have seen instances in which iron given before dewormification did not produce much effect but after dewormification the stores held in the body were rapidly utilised and quick improvement in anaemia resulted without any subsequent administration of iron. It may be argued that this was a delayed respone to iron therapy. This however was not shown in a control, Curve 'D', in which dewormification was not produced and the curve continued to run more or less flat.



Graph 4.—Response to intravenous iron after de-wormification.

These observations are too few to make any dogmatic conclusion but if they would stimulate other workers to make observations on the same lines the purpose of this paper would be amply fulfilled.

SUMMARY

(1) Evidence is shown that Ancylostome duodenale produces anaemia which in 80% cases, is of the iron deficiency type.

(2) That there is no definite relationship between the degree of anaemia and number of worms present in the system.

(3) Anaemia is probably due to the toxic action of some substance elaborated by the worms which prevents the utilisation of the Iron.

(4) Iron therapy parentral or oral before dewormification is not very effective.

(5) After dewormification quick response is produced both by parentral and oral Iron therapy.

MEDICAL PROGRESS

MANAGEMENT OF WATER AND SALT DEPLETION IN SURGICAL PATIENTS

K. N. Udupa *

Surgeons have recognised the advances recently made by various investigators in the field of dehydration. Unfortunately their enthusiasm in treating, indiscriminately, all cases of dehydration, without paying much attention to the ætiological factors responsible for it, results in more harm than benefit. Deaths due to hypostatic pneumonia during the first few days after operation, are still met with, which can be attributed to the haphazard treatment of dehydration and debility with glucose or glucose saline. Hence a very careful observation of the causes of dehydration and its appropriate correction is a pre-requisite for the administration of fluids.

The term 'dehydration' is really a misnomer, and should be referred to as water and/or salt depletion depending upon the causative factors. Marriot[6] has emphasised that such a dehydration can be caused by (1) pure water depletion, (2) pure salt depletion, and (3) mixed water and salt depletion.

WATER METABOLISM.

Water, according to Gamble[5], comprises 70 per cent of the body weight. It is contained in three reservoirs (Tab. 1.), in the blood, in the interstitial tissue and in the cells. Water in the blood and in the interstitial tissue is identical and referred to as extra-cellular fluid, while that within the cells is called intracellular. The sodium and chloride-ions are the main electrolytic constituents of the extra-cellular fluid, while potassium and phosphate are the main electrolytes of intracellular fluids. (See Diagram 1.)

TABLE 1. *Showing Body Fluid Compartments.* (*After Marriot*).

a	b	c
Extra	cellular fluid	Intracellular fluid
5%	15%	50%

(a.)	Vascular Fluid Plasma ..	5%	(body weight.)	Extracellular fluid
(b.)	Interstitial Fluid ..	15%	,, ,,	
(c.)	Cell Fluid	50%	,, ,,	Intracellular fluid.

---

* Civil Surgeon, Mandi District, Mandi, Hirachal Pradesh.

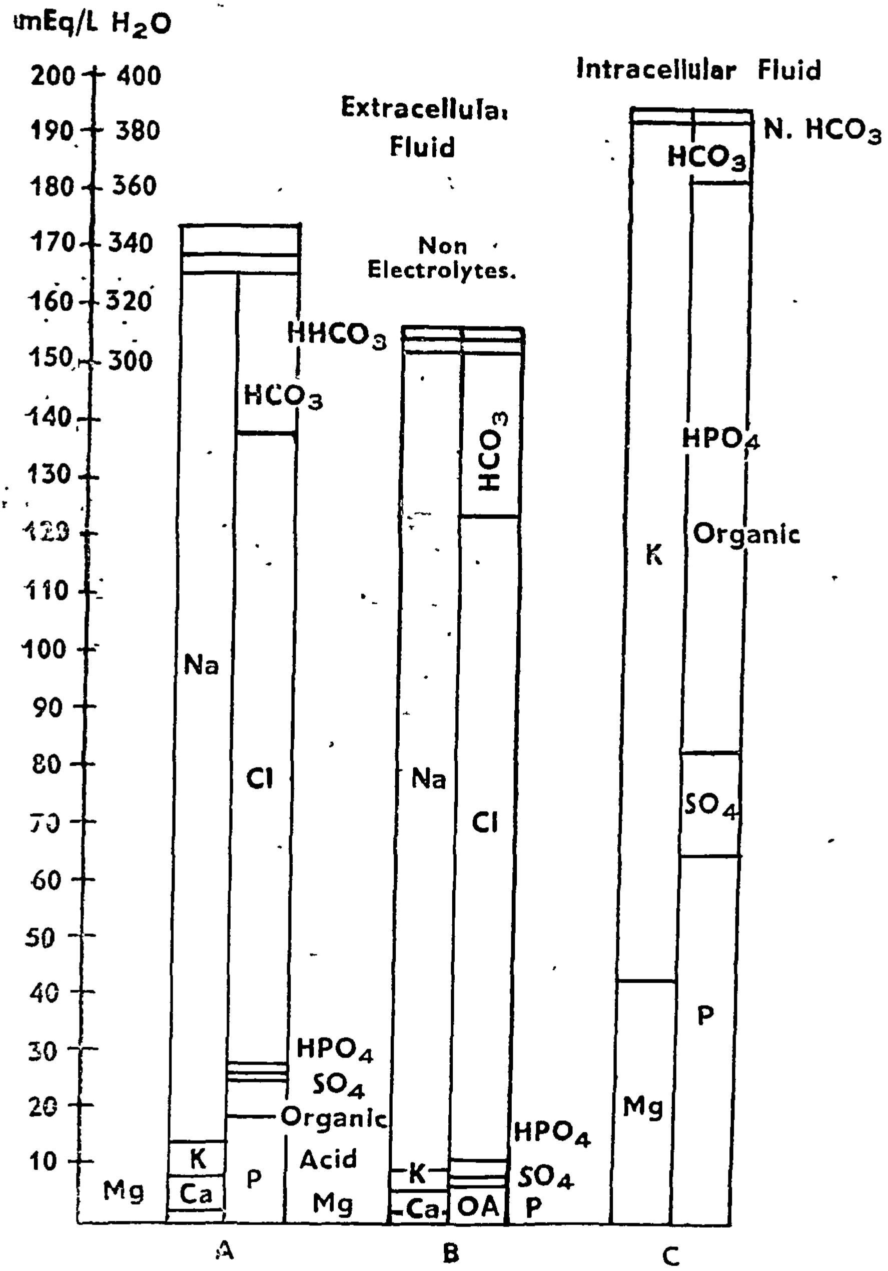


Diagram 1.—Showing the Chemical anatomy of extra-cellular fluid (blood plasma and interstitial fluid) and of cell fluid, in terms of acid-base equivalence. (After Gamble).

A.—Blood Plasma. B.—Interstitial Fluid. C.—Cell Fluid.
P.—Denotes Proteins. O. A.—Denotes Organic Acid.

Normally, there is always a free exchange of fluids within the two sub-compartments of extra-cellular fluid, namely, the vascular and the interstitial. In the arteriolar end of every capillary there is a hydrostatic pressure of fluid which exceeds the osmotic pressure of plasma proteins. Therefore fluid passes from the capillary into the interstitial space (Diag. 2).

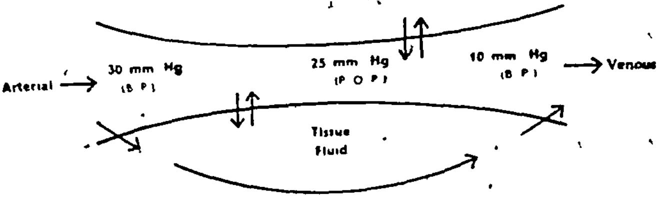


Diagram 2.—Showing fluid interchange between blood and tissue spaces (After Wright).
B. P.—Blood Pressure. P. O. P.—Plasma Osmotic Pressure.

While at the venous end of the capillaries the osmotic pressure of plasma proteins exceeds that of the hydrostatic pressure, causing the fluid from the interstitial space to be sucked into the capillaries. Due to these factors, to-and-fro movements of the fluid between vascular and interstitial tissue are so balanced that fluid constituents of both the compartments remain the same in normal individuals. If the hydrostatic pressure is increased at the venous end of the capillaries, as in congestive heart failure, or if the osmotic pressure of plasma proteins is decreased, as in hypoproteinæmia, water is retained in the interstitial compartment and œdema results.

Osmotic isotonicity of all the compartments is of prime importance for the proper function of the body, especially the cells. The cell membrane being freely permeable to water, any imbalance in the osmotic pressure results in water being either sucked in or forced into the cells.

Sources of Water.

Ordinarily, water is available for the body from the ingestion of food and water as such. According to Coller and Maddock[2] the usual daily food yields about 1,000 to 1,500 cc. of water, and drinking water and beverages combined account for a daily intake of about 1,500 to 2,500 cc. This intake is, however, subject to the individual habits and the external temperature prevailing. Coller and Maddock, from their studies came to the conclusion that about 2,500 cc. is the average quantity of water intake per day. Water is also added to the body from oxidation of carbohydrates and fats, which according to Rowntree[9] comes to about 500 cc. Therefore, the total intake of water, including water from oxidation processes, in an average normal person with moderate external temperature, is about 3,000 to 4,500 cc. daily.

Water Loss.

Water is lost from the body by the following routes :—

(1) *Insensible Loss.* There is constant vaporisation of water through the lungs and skin, which, according to Fuge and Hogg[4] in

uncomplicated surgical patients, amounts to 1,154 cc. to 1,830 cc. the average being 1,457 cc. observed in 12 patients. In the presence of fever or increased metabolism, as in hyperthyroidism, this amount may reach 2,000 cc. to 3,000 cc. per twenty-four hours. The salt content of such an insensible loss of fluid is negligible and for all practical purposes this fluid loss can be treated as distilled water.

(2) *Sensible Loss.* (*a*) Through sweat glands. Whenever the body temperature is raised, the sweat glands begin to function actively and the fluid is liberated on the surface of the body for evaporation, so that the body heat may be dissipated. Large amount of fluids may be eliminated through this channel and in the tropics may amount to about 13 litres per day. This sweat constitutes nothing but a hypotonic saline solution with a concentration of sodium chloride of about 1 to 5 Gm. per litre varying with individuals (average being about 2 Gm. per litre or 0.2 per cent).

(*b*) By the kidneys. The excretion of urine can be divided for practical purposes in two parts. (i) The minimum volume for excretion of waste products (about 35 Gm. daily) which is about 500 cc. per day and (ii) the surplus water taken by mouth after deducting the requirements of the skin, lungs and the gastro-intestinal tract, which usually is about 1,000 cc. per day in a normal healthy person. The minimum volume of excretion of urine depends upon the concentrating power of the kidneys and the amount of waste products which have to be eliminated. A diminished concentrating power exists in children, in the aged, in those suffering from chronic nephritis and in other pathological conditions like obstructive lesions of the urinary tract, especially prostatic obstruction. In old people the concentration power of the kidneys is decreased and large amounts of fluid are excreted by them to get rid of the waste products. The natural consequence of this is that the urine contains very little solids and the specific gravity is low. In such cases, if the urine excreted is little, good ground is afforded for the development of uræmia.

The quantity of waste products is more than normal in those people who have a greater metabolic rate. Then also they have to pass more urine, than the minimum necessary, to eliminate the waste materials collected in the body. Thus in children, in febrile conditions and in conditions, like hyperthyroidism, more urine is passed. In children, because of the loss of concentrating power of the kidneys and the presence of more waste products in them, they have to pass proportionately more urine than adults. As emphasised by Marriot[6] the storage of water is much less in them and the quantity excreted is greater, therefore they tolerate any abnormal loss of water or salt from their body poorly.

(*c*) Gastrointestinal Tract. The large amount of water loss into the gastrointestinal canal, excreted as saliva, gastric juice, bile, pancreatic juice and succus entericus, is usually not appreciated. The total daily loss of such fluid for 24 hours comes upto 7,500 cc. to 10,000 cc. according to Rowntree[4], and about 8,200 cc. according to Gamble[5], while the total plasma volume is only 3,500 cc. Gamble made the following estimation of various secretions for 24 hours :—

Saliva	1500 cc.
Bile	500 cc.
Succus	3000 cc.
Gastric Juice	2500 cc.
Pancreatic Juice	700 cc.
Total	8200 cc.
Blood Plasma Volume	3500 cc.

After serving their purpose these fluids are passed on into the distal portion of the intestinal canal where they are absorbed into the blood through the lower ileum or proximal colon, leaving behind only 150 cc. of fluid to pass out through the fæces. Mason and Zintel[8] have specially emphasised the fact that any disturbance in the circulation of the gastro-intestinal secretion means a great loss of fluid and salt from the body. They state "This gastrointestinal circulation represents two to three times the average quantity of fluid taken by mouth in 24 hours. It is equal in amount to twice the volume of the blood-plasma. To the surgeon, disturbance in the gastrointestinal circulation as occurs in vomiting, constant suction drainage from the stomach or intestine, gastric and duodenal fistula, diarrhœa and other disorders, are of great significance."

The following is the resume of water intake and output for twenty-four hours in normal persons living in temperate climates. (Tab. 2).

TABLE 2. *Diagrams Showing A Fluid Intake and B Fluid Output During a Twenty-four Hour Period in a Normal Individual.*

A		B	
Water of oxidation	500 cc.	Water in fæces	200 cc.
		Water as sweat	300 cc.
Water in solid food	1000 cc.	Water as insensible loss via lungs & skin	1000 cc.
Liquids taken orally	1500 cc.	Water loss via kidneys as urine	1500 cc.
Total intake	3000 cc.	Total output	3000 cc.

Intake.		Output.	
Food	1000–1500 c.c.	Insensible Loss ..	1000–1500 c.c.
Water & Beverages	1500–2500 c.c.	Sweat	300–600 c.c.
Water from Oxidation	500 c.c.	Urine	1500–2000 c.c.
Total	3000–4500 c.c.	Total	3000 4500 c.c.

PURE WATER DEPLETION

Causes :—

(1). Greatly enfeebled persons, either due to medical or surgical causes do not feel much thirsty and hence the fluid intake is low.

(2) Dysphagia due to any lesion rendering the person unable to drink water, e.g., quinsy, cancer of the œsophagus etc.

(3) Conditions where water is not available or not given intentionally due to ignorance, etc.

Signs and Symptoms.—Thirst is the first symptom of pure water depletion. Dryness of the mouth and tongue soon follow due to the decreased salivation, by which swallowing of dry foods become impossible. Urine volume falls to the minimum of 500 cc. or less. Marriot[6] states "given a normal kidney and a solute load, the urine volume will be approximately 500 cc., the contents of dissolved solids 6-8 Gm. per 100 cc., the specific gravity will rise to more than 1030 and may even exceed 1040. The kidneys are faced with the dilemma of having to attempt the simultaneous excretion of waste and salt and yet to economise water."

Loss of weight, a feeling of weakness, a pinched face, a dry skin, temperamental peculiarities, confusion of mind and death are usually due to uræmia.

Principles of Treatment.—Since the symptoms are mainly due to loss of water from the body by insensible loss of 1,000 cc. through vaporisation and by a minimum quantity of urine, *i.e.*, 500 cc. through the kidney, our aim should be to replace water and water only by any of the available routes. To this may be conveniently added glucose which in the end is metabolised into water and carbon dioxide, in addition to its ability to supply energy to the body in the easiest way. The water thus produced will be added to the body requirement while the carbon dioxide will be excreted through the lungs without any special effort. Therefore, pure water or glucose water should be given whenever there are signs and symptoms of pure water loss. This can be given by mouth, per rectum or by the intravenous route.

SALT METABOLISM

Barlett *et al*[1] have estimated the total sodium chloride content of the body as being 1/400th, of the body weight. Thus, a man weighing 154 lb. or 11 stones will have about 6 oz. or 175 Gm. of salt in his body. Out of the total quantity two-thirds is in the plasma and intertitial tissue fluid and the rest is in the alimentary secretions. As Gamble[5] has emphasised, one can understand from the figures that the sodium and chloride contents of the plasma and the interstitial fluid are almost indentical except for the presence of some extra proteins in the plasma. On the other hand the chemical constituents of the intracellular fluid are quite different, and as already explained, its chief constituents are potassium and phosphates. Whatever may be the differences in the chemical composition of the various fluids, the osmotic pressure always remains the same in normal persons. Any change in the osmotic pressure in any of these fluids due to abnormal salts or fluid loss, is followed by the water being pushed in or sucked out from the surrounding compartments to maintain a uniform pressure.

Hence the main function of these chemical constituents is to maintain a constant osmotic pressure and secondly to maintain a constant acid base balance. Sodium ions are of greater importance than the chloride ions as the latter can be easily replaced by bicarbonate ions which are always readily available in the blood from the tissue-metabolism. Therefore, dehydration will be more pronounced in sodium loss than in chloride loss.

Sources of Salt. According to Coller and Maddock[2], about 4 to 8 Gm. of salt are ingested by a normal person. Out of these about 3 to 6 Gm. come from the salt added to the meals to make them palatable. The remaining, *i.e.*, 1 to 2 Gm., is found as the natural constituent of food. In addition to this, about 8 to 10 Gm. of salts are recirculated through the gastro-intestinal canal; because, as already stated, about 8 to 10 litres of salt containing fluid is daily excreted into the gastro-intestinal canal through various alimentary secretions. Sodium and chloride in a variable quantity are the main constituents of these secretions in addition to water (see table below).

TABLE.—*Showing Variations in Quantity of Sodium and Chloride in Secretions.* (*After Coller and Maddock*).

Secretions	Total Base.	Cl.	HCO 3
Gastric Juice	40 M.Eq./L	160 M Eq/L	——
Bile	182 ,,	90 ,,	45M .Eq/L
Pancreatic Juice	168 ,,	115 ,,	45 ,,
Succus Entericus (Jejunum) ..	155 ,,	150 ,,	20 ,,
Blood Serum	164 ,,	110 ,,	22 ,,

Excretion of Salt.

(a) Gastro-intestinal canal. Almost all the above mentioned quantities of salt found in the various secretions of the digestive tract are reabsorbed into the blood leaving behind only about 0.2 Gm. of sodium chloride in the fæces.

(b) Skin. From the skin the salt is excreted in various quantities from 0.25 to 0.40 Gm. per day through insensible loss and sweat which is a very negligible amount. This quantity varies from person to person and from place to place. Those living in the tropics excrete much less salt through this route than those living in the temperate climates.

But on a hot humid day and in a person leading an active life this salt loss may be as high as 2.0 Gm. per day.

(3) The kidneys excrete the excess of sodium and chloride remaining after the fæces and skin loss have been deducted from the total intake. For example, on an ordinary day, if the oral intake of sodium chloride is 5 Gm., the kidneys will excrete about 4.5 Gm. of it in about 1,600 cc. of urine. or, in other words, 3 Gm. of sodium chloride per litre of urine, the remaining 0.5 Gm. finding its way out through the sweat and fæces. (skin 0.25 Gm. and fæces about 0.25 Gm.).

PURE SALT DEPLETIONS

This condition can occur whenever there is abnormal salt loss from the skin, gastrointestinal canal or kidney. The salt is always lost from the body along with the water and if the water or glucose water is liberally given to such patients without giving salt, then secondary dehydration due to pure salt depletion occurs. Excessive sweating on a hot humid day, vomiting, diarrhœa, and constant suction drainage of the gastrointestinal canal, biliary or intestinal fistula and Addison's disease are some of the examples of this condition. It is obvious that smaller losses occurring over long periods can also cause some depletion, more so, if the salt intake is lowered.

(1) In the sweat, the salt is excreted as a hypotonic solution with about 0.2 per cent sodium chloride. Since the sweat is derived from the plasma, for each litre of sweat, a litre of water is lost from the body ; because the amount of salt in the sweat is less than that of the plasma the excess of salt thus present is excreted through the kidneys. Hence for every litre of sweat there is a loss of a litre of isotonic saline through the sweat. In replacing water and salts lost by profuse sweating, the deficiency may be made good by oral administration of 0.2 per cent of salt solution. If pure water only is taken by mouth and if the sweating has been excessive, all signs and symptoms of salt-loss like lassitude, apathy, weakness, headache and cramps develop. If the fluid is to be administered parenterally, then physiologic saline solution serve very well. In such patients physiologic glucose (5 per cent) is unsatiss factory, in that it does not supply the required salts.

(2). Through the gastro-intestinal canal a patient can loose his salts within a space of a few minutes or an hour or two, as in acute ptomaine poisoning. In vomiting, a large amount of chlorides are excreted through the vomited matter in addition to the loss of sodium ions through it to some extent. The remaining plasma sodium unites with the readily available H_2CO_3 and is excreted through the kidneys as $NaHCO_3$, thus decreasing the tendency for the development of alkalæmia. If the vomiting is excessive or prolonged, the patient is bound to develop alkalæmia. The plasma volume becomes less and plasma carbon dioxide combining power increases. Chlorides in the urine will be considerably decreased or may become absent.

When the fluid is lost from the small intestine or colon as in diarrhœa, there occurs a loss of fluid in which sodium tends to predominate. Therefore the plasma chlorides may be normal or increased and the bicarbonate content will decrease. When the sodium ion is lost from the body it cannot be replaced by any ions. Hence in order to keep the acid base balance at the normal level, an excess of chlorides are excreted from the body. The net result of these changes is the decrease in the concentration of these salts kept in a isotonic level. The body excretes the excess amounts of water, thus decreasing the total body water and producing a secondary dehydration. (Table. 3.)

TABLE 3 *Showing the Osmotic Pressure in (I) Pure Water Depletion (Primary or Simple Dehydration) and (II) Pure Salt Depletion (Secondary or Extracellular Dehydration) (After Marriot).*

(I)				(II)		
a	b	c	←Normal→ level	a	b	c
Ex	tracellular fluid	Intracellular fluid		Ex	tracellular fluid	Intracellular fluid

a. Vascular b. Interstitial c. Cellular.

Therefore, secondary dehydration is more apt to occur in association with sodium loss than after chloride depletion. If the sodium continues to be lost from the body, the plasma volume becomes decreased. As already explained, the plasma carbon dioxide combining power decreases and the patient develops acidosis. The urinary chlorides again become less or absent in the later stages.

In cases of duodenal fistula, chloride and sodium ions are lost in equal quantities and in biliary fistula, the sodium ions are lost in greater quantity than the chloride ions. While replacing all these salts and fluids, according to Gamble[5], isotonic saline should be given either by mouth or by the intravenous route, volume for volume, of the fluid lost through the gastro-intestinal canal, irrespective of whether the chlorides are lost in excess of sodium as in vomiting or sodium ions are lost in excess of chlorides as in diarrhœa: the kidneys will take care of the excess quantity of sodium or chlorides injected into the blood and adjust these ions according to the requirements of the body and excrete the quantities that are in excess.

(3). In Addison's disease the kidneys excrete large quantities of sodium and chlorides due to which the plasma sodium content falls below normal. Unless the sodium chloride is replaced, these patients suffer from all the symptoms of salt depletion in addition to the signs and symptoms of the original disease. These symptoms disappear as soon as they are kept in positive salt balance by the administration of large doses of sodium chloride by mouth or intravenously.

Signs and Symptoms of Pure Salt Loss. Marriott[7] has described in detail the effect of pure salt loss. He ascribed the manifestations of pure salt loss as being mainly due to two factors. (1) Those due to loss of osmotic pressure and those (2) due to disturbance in the acid-base balance. Of these two factors, the loss of osmotic pressure is of greater importance. Those who are desirous of obtaining further details are referred to the original article by Marriot[7] on the subject.

Manifestations of Salt Loss due to osmotic pressure decrease :—

(1) A feeling of exhaustion, fatigue and weakness may have been experienced by any one who has had a chance to perspire heavily on a hot summer day. The same condition leads to the state termed as "heat exhaustion" if of a severe nature. The examination of the urine of such persons will show the absence of chlorides.

(2) Headache and giddiness are often present due to low blood pressure resulting from secondary dehydration produced by salt depletion.

(3) An absence of thirst is one of the important signs of salt depletion, by which dehydration produced by pure water depletion could be differentiated.

(4) Normal urine volume may be noted till the last stages; if the patient with salt depletion goes on drinking water, the urine volume remains normal or may be increased, as the blood has an excess of water rather than of salt.

(5) Anorexia, nausea and vomiting develop in the late stages and aggravate the condition.

(6) Cramps are very common in salt depletion cases.

(7) Changes in appearance and mental confusion occur n the late stages.

Changes in the blood. Plasma sodium chloride remains unchanged in the early stages, because the kidneys try to retain all the salt which would have passed out into the urine. On this account the urine may not show any chloride content. Hence the test for retention of chloride content of the plasma is not a very satisfactory one for the detection of salt depletion from the body.

(a) Disturbances due to changes in the osmotic pressure.

There is a remarkable decrease in the circulating plasma volume which may be as much as 20-30 per cent in severe cases, for, as soon as the salt is expelled from the blood, the excess of fluid that remains in the blood is excreted by the kidneys in order to maintain the isotonicity of blood (*i.e.*, osmotic pressure). Loss of fluid from the plasma produces hæmoconcentration. Blood pressure falls and all the signs and symptoms of peripheral circulatory failure occur and death is usually due to the development of the latter condition.

(b) Disturbances due to acid balance are not has important as those due to disturbed osmotic pressure to which reference has already been made. Those symptoms, developing on account of changes in the acid-base balance, are marred by the other main symptoms. As already stressed, patients loose more chlorides through vomiting, hence they are more prone to the development of alkalosis. On the other hand those suffering from diarrhœa develop symptoms of acidosis due to the greater loss of sodium ions than of chloride ions.

(c) One of the most important effects of salt depletion is on intestinal motility. From the surgeon's point of view this has been thoroughly discussed by Streenten[10] recently. He has proved beyond doubt both experimentally and clinically that lack of sodium and chlorides in the blood greatly interferes with the motility of the intestines giving rise to paralytic ileus. Experimentally, in the isolated loops of intestine of rabbits, guinea pigs and of human beings immersed in Tyrode's solution of varying sodium chloride content, he found a reduction in the propulsive movements of the intestines and also a decrease in the response to neostigmine and acetylcholine treatment. This action of sodium chloride of producing such an effect on the intestinal loop is not due to its capability of maintaining the normal osmotic pressure only, as the impairment of such propulsive movements persists even if the osmotic pressure is brought to normal by the judicious use of dextrose or sucrose. The presence of certain concentrations of chloride ions are as important as those of sodium, since replacement of either of the two with various other salts did impair the movements of the intestines.

Therefore, in patients with paralytic ileus and in whom the plasma sodium chloride is found greatly decreased and urine chloride is found absent, the correction of these deficiencies by appropriate saline therapy must be made before any treatment with neostigmine or acetylcholine is instituted. He also cited a typical case history of a patient with paralytic ileus developing after an abdominal operation. In this patient whenever the urine chloride was made positive by the administration of large quantities of intravenous saline, the peristaltic movements of the intestine became active and the patient responded well to the use of prostigmine. It is also my experience in a large number of abdominal operations performed during the past years that whenever any patient with an abdominal operation received adequate amounts of normal saline, as determined by the urine chloride estimation method, in the immediate post-operative period, there is no chance of development of paralytic ileus. Even if a patient develops some of the minor symptoms of impending paralytic ileus, these are immediately relieved by the use of any of the parasympatheticomimetic drugs like prostigmine, carbachol etc. Therefore every surgeon who comes across a patient with paralytic ileus must bear these factors in mind before he plans any active treatment.

Laboratory Diagnosis of Pure Salt Depletion :—

The test for the detection of plasma chlorides is not a very reliable indication of the underlying condition. As already discussed, the kidneys always try to keep up the concentration of sodium chlorides in the blood at a normal level by preventing the excretion of sodium chloride through the urine. Therefore the test can only show if there is a gross loss of salt from the blood. Therefore the urine chloride estimation test of Fantus is an important and a simple test which should help us to know whether a given patient is suffering from pure depletion or not. This test can be done within a minute or two and is much simpler than many other chemical tests of urine. If the salt is found below 3 grammes per litre of urine, then one should infer that the patient is suffering from salt loss. In Addison's disease and during saline therapy the urine may contain larger amounts of chlorides.

Technique and Interpretations of Fantus Test

Requirements :

1. Potassium Chromate solution 20%
2. Silver Nitrate solution 2.9%
3. Distilled water
4. Test tubes.
5. A small pasteur pipette.

Marriot[7] has described the technique which is as follows, and the same method has been followed by the author.

"Ten drops of urine are measured into the test tube. The pipette is rinsed in water and one drop of potassium chromate solution (indicator) is added. The pipette is again rinsed and the silver nitrate solution is added drop by drop and the tube lightly shaken after the addition of each drop. The end point is determined by the sharp colour change from yellow to brown. The number of drops required to produce the colour change gives the concentration of chlorides in the urine expressed in grammes of sodium chloride per litre of urine. Example :—5 drops are equal to 5 Gm. of sodium chloride per litre of urine. It is important to make a preliminary test with distilled water to make sure that there is no contamination of the chromate solution with the chlorides."

In the test one should observe the following precautions :—(a) Use the same pipette for carrying out the test. (b) See that the drops of urine and the solutions are of equal size. (c) If the first drop of silver nitrate solution changes the yellow colour to brown, then it can be safely presumed that chlorides are absent in the urine. Normally, a person is likely to pass about 3 to 5 Gm. of salt per litre.

Principles of Treatment:—

The general principle is to replace salt in the form of salt water by mouth or rectum or isotonic saline solution through subcutaneous route or intravenous route, till sufficient quantity of chlorides appear in the urine. It is immaterial whether the salt loss is due to vomitings or to diarrhœas and whether the patient is suffering from alkalosis or acidosis. The replacement of normal saline should be equal to the quantity lost through both the routes.

DIFFERENCES BETWEEN PURE WATER AND PURE SALT DEPLETION

In pure water depletion the water is lost from the extracellular (blood and interstitial tissue) compartment and therefore the osmotic pressure of this compartment is raised. The result is that the fluid from the adjacent compartment namely intracellular compartment is automatically extracted. Therefore, the loss of water is mainly felt in the intracellular compartment and not much in the extracellular (see Tab. 3). In this condition symptoms like thirst, dry mouth and tongue, scanty micturition, are greatly felt. While in pure salt depletion, salts are lost at first from the extracellular compartment. The result is that the osmotic pressure of this compartment becomes less. Therefore, in order to keep up the normal osmotic pressure of the blood, the kidneys try to excrete the excess of water from the body. The result is that there is considerable decrease in the volume of extracellular fluid and the volume of intracellular fluid remains normal. Therefore, in salt depletion there is no feeling of thirst or dry mouth. The urine quantity remains normal or in excess, till the later stages. Symptoms like exhaustion, weakness, cramps, headache, giddiness, low blood pressure, are greatly felt. The total plasma volume becomes less and hæmo-concentration takes place, which leads to the development of signs and symptoms of shock. One should be aware of these factors before actually undertaking treatment for dehydration.

MIXED WATER AND SALT LOSS

There is reduction of both water and salt by loss through various secretions, in vomiting, diarrhœa or excessive sweating (heat exhaustion), without any replacement of water or salt. In this condition signs and symptoms of water loss predominate, because all the secretions lost are either isotonic or hypotonic, in addition to constant insensible water loss from the body. Therefore, thirst, dry mouth and oliguria are more pronounced, although symptoms of pure salt depletion like weakness, apathy, giddiness, cramps, low blood pressure etc., are also constant features. Diagnosis of this condition is reached by the history, signs and symptoms and urine chloride concentration test. The replacement should be as balanced as possible with the use of isotonic saline to replenish salt loss and isotonic glucose solution to replace water loss.

Amongst all these three causative factors, in practice, dehydration due to pure salt loss or mixed water and salt loss are very common, because of the many causes of vomiting and diarrhœa. For example, vomiting can occur in almost all the acute abdominal conditions, like appendicitis, peritonitis after anæsthesia, in pregnancy, uræmia, diabetes etc. Similarly the causes of diarrhœas are innumerable, like cholera, sprue, ptomaine poisoning, dysenteries, malignant diseases of the gastro intestinal tract etc.

TREATMENT IN GENERAL

Pre-operative fluid replacement :—

For normal surgical patients who are not suffering from dehydration of any type, Coller and Maddock[2], have suggested the most practical method of determining the quantity of fluid to be given during a twenty-four hour period.

Uncomplicated cases.

Water for vaporisation (insensible loss)	1000 to 1500 cc.
Water for urine	1000 to 1500 cc.
Total	2000 to 3000 cc.

Complicated cases with fever or on a hot humid day.

Water for vaporisation	2000 to 2500 cc
Water for urine	1000 to 1500 cc.
Total	3000 to 4000 cc.

On the average all the usual surgical patients require about 3000 cc. for a 24-hour period. This amount is required by a patient who is not dehydrated and who does not lose any fluid through any abnormal route. In a patient who is already dehydrated before operation, the fluid balance must be corrected before any attempt is made to perform operations. In the past decade or two, considerable stress was laid on the correction of water and salt deficiencies of all patients undergoing surgical procedure and it is indeed due to the investigations of Coller and Maddock[2] that adequate attention is paid to this therapy. Due to such investigations the mortality rate in conditions involving acute disturbances of fluid and salt balance like congenital pyloric stenosis, intestinal obstruction, etc., has greatly decreased, so much so, that acute abdominal emergencies requiring immediate operation, except vascular emergencies, have become much less; because, except for the latter conditions, where immediate operation is indicated, the delay incurred while correcting the fluid and salt balance in these so-called emergency patients, within 6 to 12 hours before operation, has considerably decreased the mortality rate in many of the well-known hospitals. Therefore, as already stated, correction of dehydration must be made before any operations are undertaken. The diagnosis of dehydration should be made by the various clinical manifestations like thirst, dry mouth and tongue, urine volume, etc. With the help of such signs one can roughly make out whether the patient is suffering from dehydration of pure water or salt depletion or from both. The history of the patient will throw much light on the differentiation of the various types of dehydration. Still in cases of doubt it becomes necessary to estimate the total quantity of urine in 24 hours or in cases of emergency even in six hours. Examination of the urine for the determination of specific gravity and also the determination of urine chlorides in grammes per litre will help a lot to make out what type of dehydration the given patient is suffering from. The replacement of fluid should be planned accordingly. As regards the determination of the quantity of fluid to be given in any form, Coller and Maddock[2] found that in extreme dehydration there is a fluid loss corresponding to 6 per cent of the body weight. On this basis they concluded that in extreme dehydration 6 per cent of body weight in fluid must be given to restore hydration. The following table is given by Maddock and Coller for calculation.

Amounts equalling 6.0 per cent of body weight.

Body weight.	6% in cc.
22 lbs.	600 cc.
44 lbs.	1200 cc.
132 lbs.	3600 cc.
176 lbs.	4800 cc.

These amounts of fluid are necessary over and above the usual daily requirements of fluids of 3000 cc. However, the additional amount required to hydrate the patient may not be given in one day, particularly, in aged people or in those with cardiac insufficiency diseases. In most cases, the additional amount may be given in two days. In addition to this, if the patient continues to loose fluids and salt through vomiting etc., the amount must be replaced by normal saline, volume by volume, in addition to the above fluid amounts.

Fluids during operations:—

In the operation theatre iteself, the patient, in addition to his blood loss during operation, also looses a large amount of fluid by insensible loss and also through visible perspiration, especially if the operation is prolonged and performed on a hot humid day. Therefore, in such prolonged operations it is advisable to start intravenous physiologic saline during operation so that this deficiency of fluid and salt loss can be replaced there. This amount should not be calculated along with the fluid requirements for the whole day. There is another advantage of starting intravenous saline just before performing the operation, because should there be any unforeseen accident during the operation or even without it if the condition of the patient deteriorates during operation, blood or plasma transfusion could immediately be given through the same needle already in the vein. Therefore, the starting of intravenous saline in all major operations has great advantages and very few disadvantages.

Post-operative fluid replacement:—

The principle of water and salt therapy in the post-operative period is the same as that in the pre-operative periods, i.e., to an ordinary surgical patient, about 3,000 cc. water and about 4 to 8 Gm. of salt are required per twenty-four hours. In addition to this, any abnormal loss of fluid during the post-operative period such as excessive vomiting, too much perspiration or any other abnormal drainage from the wounds or gastro-intestinal canal, must be carefully measured as far as possible and an equivalent amount of physiologic saline solution must be added to the normal requirements of fluid and salt.

If it has not been possible to measure accurately the amount of fluid lost through the vomiting etc., then the resort to clinical and laboratory examinations should be made. In laboratory examinations the total urine volume and its specific gravity and also the urine chlorides and plasma chlorides estimation tests should be carried out. However, recently, Van Slyke and Evans[11] have investigated the relationship between urinary chloride excretion and dehydration and salt deprivation in human subjects. On the basis of these studies they have suggested that provided the kidney function and adrenal functions are normal, water and salt balance may be considered as being properly maintained, if the daily urine volume reaches 1,500 cc. and if the salt concentration in the urine approximates 3 grammes per litre. Here the determination of specific gravity also will help to know whether the kidneys are normal or not.

Recently, however, Coller[3] and his co-workers found that in the immediate post-operative period, i.e., from 2 to 5 days there is a fall in the urine chloride excretion in almost all cases. This natural tendency to retention of sodium chloride in the body in the immediate post-operative period is related to inflammatory reactions to injury, and now there is ample evidence to show that there is an accumulation of large quantities of chlorides in damaged tissues. On account of these facts, salt should not be given in large quantities in the immediate post-operative period, based on the urine chloride estimation alone, unless there is much loss of chlorides in the secretion of the gastro-intestinal canal or sweating. To sum up the discussion regarding the administration of fluids it has been found that about 2,500 cc. (5 lb.) of 5 per cent or isotonic glucose solution containing 125 Gm. (about 4 oz.) of glucose and 500 cc.

(1 lb.) of isotonic salt solution containing 4.5 Gm. of salt are required for an uncomplicated surgical case for 24 hours. The routes by which these fluids can be administered depend upon the condition of the patient and the nature of operation. All the quantity of abnormal loss of fluid should be added to the above quantities as normal saline. The usual practice of giving large amounts of glucose in saline is not desirable and it is not physiological too, because, the mixture of two isotonic solutions becomes hypertonic and may furnish too much salt to the body, with attending dangers which will be discussed later. Therefore, as far as possible, only isotonic solutions should be introduced into the blood and if necessary half norma lsaline and half normal glucose solution may be mixed together. While giving intravenous glucose it is always better to add vitamin B_1 (thiamine hydrochloride) to assist the better utilisation of glucose and other water soluble vitamins like vitamin C.

EFFECTS OF EXCESS OF WATER AND SALT ADMINISTRATION

If too much water is introduced in the form of pure water or glucose water through any route, there is a danger of developing water intoxication which may lead to death.. Regurgitation of water into the trachea producing aspiration pneumonia especially in old people is not uncommon. Similarly, a healthy normal individual can handle even 30 to 40 grammes of salt daily without developing any toxic symptoms, for the kidneys are able to excrete the excess of salt through urine up to 2 per cent concentration. However surgical patients who are seriously ill after operation may not be able to cope with all the salt introduced into the blood. Therefore, any excess of salt if given to surgical patients is retained by the interstitial tissue along with the water to make it isotonic resulting in edema. This can easily develop in the patients who are already suffering from protein starvation and with a low serum albumin. It can also be easily produced in patients with general malnutrition, chronic sepsis, hæmorrhage, profuse serous drainage etc. There is every evidence to show that the greater the severity of these predisposing factors, the less salt solution it requires to produce œdema. General external œdema is the visible indication of œdema with harmful effects on all the internal organs and therefore œdema of the brain and lungs is not an unusual consequence of excessive salt intake. Excessive salt intake in the immediate post-operative period can also produce œdema in the stoma of gastroenterostomy and similar anastomoses. Therefore, excess of salt and water intake should always be avoided.

ROUTES OF ADMINISTRATION

By Mouth. Fluid by mouth is the most natural and physiological means of administration. As far as possible this route should be used, unless there are some specific contra-indications. In our hospital it is the practice to give a bottle of fluid every morning containing the required amount of water, glucose and salt, which the patient must finish before bedtime. This practice has greatly helped us to maintain a proper water and salt balance in various surgical patients who can take fluid by mouth. For the unconscious patient intra-gastric drip with a Ryle's tube may be tried and serves the purpose well. However, in many other conditions fluid by mouth cannot be given. In such patients the following routes may be adopted.

Continuous Rectal Drip. In our hands the continuous rectal drip of tap water or saline has proved very useful in the immediate post-operative period. Immediately after the operation especially under general anæsthesia the patient may not regain consciousness for the whole day. Moreover, such patients have a tendency to vomit for the first day or two. Here, continuous rectal saline or water is the most valuable means, next to mouth, for maintaining a proper water and salt balance. It is an easy method, for it requires no special sterilisation, is easy to prepare and administer and is not accompanied by any reactions.

Subcutaneous Route. Only normal saline could be introduced safely by this route and not the isotonic glucose solution. The latter sometimes produces painful swelling in the area of administration and may also produce sloughing of the tissues. However, recently, this route has fallen into disrepute in many hospitals except in cases of small children in whom the intravenous method is somewhat difficult.

Webb *et al*[12]. have recently demonstrated, experimentally and clinically, that only isotonic saline solution should be given by this route in cases of salt depletion and not any other solution. Moreover, since the rate of absorption of subcutaneous fluids are surprisingly slow, this route alone may not be adequate when fluid restoration is urgent. The studies indicated that in the presence of dehydration, there is much retardation in the rate of absorption in comparison to normal persons. Therefore, this route may not be relied upon for any fluid replacement in cases of emergency.

Intravenous Route. This is the most satisfactory and effective route by which various fluids can be administered directly into the blood. This route can be adopted for any number of days without any harmful effects. Many a time when there is acute dehydration, fluid administration through this route is a life-saving measure. However, this method should not be adopted in those patients who are suffering from congestive heart failure, pulmonary œdema and extensive kidney disease. Fluids can be given continuously by the drip method or by the rapid and intermittent method. It can also be given by the closed or the open method. Fluids given by continuous intravenous drip by the closed method is the most widely accepted route of fluid administration in cases of emergency, or in cases where oral method is contraindicated or not possible. Most commonly, isotonic saline solution (0.9 per cent) or isotonic glucose solution (5 per cent) are given through this route in the required quantity. In cases of emergency, blood or plasma may also be given by this route.

The rate of such fluid administration should be regularised according to the individual needs of the patient. Usually 200 to 300 cc. per hour or 40 to 50 drops per minute are the accepted method in ordinary patients. However, this rate should be changed according to the total need of fluids per 24 hours.

Case Report.

Mrs. S. aged 40 years was admitted to the hospital three days after the onset of a sudden attack of pain in the right iliac fossa. She was found to be in acute distress, temperature 101.2° F, pulse 140 per minute and feeble in character, respiration, 25 per minute. The abdomen was found very rigid, and tender. Rectal and vaginal palpation did not help any definite diagnosis. On opening the abdomen an acute diffuse peritonitis with a large amount of exudative fluid and fibrin was discovered. A big mass was also found in the right iliac fossa suggesting a perforated appendix. The abdomen was closed after placing two drainage tubes into the pelvic cavity. She was given all the chemotherapeutic and supportive treatment required. In addition, she was put on the water and salt balance chart given below. By actually measuring the output of water and salt, and by appropriate replacement as mentioned in the chart she could easily overcome her serious catastrophe within 15 days without developing many complications. This is one example cf the cases treated in our Hospital in which our successes can often be attributed to the judicious and well balanced water and salt therapy.

SUMMARY

(1) Water metabolism and the various manifestations of pure water depletion have been described. The replacement of the depletion by plain water, or water with glucose, is emphasised in pure water loss:

(2) The importance of salt and its normal circulation in the body is broadly outlined. Various causative factors of pure salt depletion like excessive sweating, vomiting, diarrhœa, are discussed.

(3) The effects of pure salt depletion on various systems, especially, causing the feeling of exhaustion, fatigue, headache, giddiness, etc., are described. The importance of administration of the required amount of salt in the immediate post-operative period to avoid the development of paralytic ileus is emphasised. The principle of treatment in pure salt depletion is administration of normal saline by the easiest available route till the urine chloride estimation test of Fantus shows the presence of at least 3 Gm. per litre of urine.

(4) The main differentiating points between pure water and pure salt depletion have been discussed. In pure water depletion the effect of loss of fluids is mainly felt in the intracellular compartment and hence

Water and Salt Balance Chart

Name of the patient:—Mrs. S. Age 40 years Sex Female
Disease : Acute Diffuse Peritonitis.
Date of Admission : 1st. Dec. 1950.

	1st Dec.	2nd Dec.	3rd Dec.	4th Dec.	5th Dec.
I Signs & Symptoms					
(1) Thirst,	++	++	++	+	+
(2) Condition of lips and tongue	Dry, +	Dry, +	Dry, +	Moist	Moist
(3) Condition of Skin	Do.	Do.	Do.	Normal	Normal
(4) Mental Condition	Nil	Nil	Nil	Nil	Nil
(5) Any other signs or symptoms	Distension abdomen	same	same	same	Nothing Particular
II Output					
(1) Urine					
(a) Total quantity	900 cc.	800 cc.	1200 cc.	1200 cc.	900 cc.
(b) Specific gravity	?	?	1011	1012	1012
(c) Urine chlorides Gm/litre,	2 Gm.	2 Gm.	Nil	2 Gm.	2 Gm.
(2) Vomit or Gastric aspiration in cc.	1800	1200	600	900	1200
(3) Fluid content of fæces in cc.	800	600	1600	900	1200
(4) Sweat in cc.	Nil	Nil	Nil	Nil	Nil
(5) Drainage through wounds in cc.	Do.	Do.	Do.	Do.	Do.
(6) Insensible loss	1000 cc.	1000 cc.	1000 cc.	1000 cc.	1000 cc.
TOTAL QUANTITY OF WATER LOSS IN CC.	4500	3600	4400	4000	4300
TOTAL QUANTITY OF SALT LOSS IN GM.	25	18	19	18	26
III Diagnosis					
Dehydration	yes	yes	yes	yes	yes
(a) water loss	—	—	—	—	—
(b) salt loss	—	—	—	—	—
(c) mixed loss	++	++	++	+	+
IV Intake					
(1) Oral					
(a) plain or glucose water	900 cc.	1200 cc.	1300 cc.	1500 cc.	1500 cc.
(b) glucose saline					
(c) water in other forms			400 cc.		
(2) per rectum					
(3) subcutaneously					
(4) Intravenously					
(a) Saline, 0.9%	3000 cc.	1800 cc.	2000 cc.	1800 cc.	2400 cc.
(b) Glucose 5%	600 cc.	500 cc.	600 cc.	600 cc.	600 cc.
(c) Glucose-saline,					
(d) Any other fluid (Protein hydrolysate)	200 cc.				
(5) Through any other routes					
TOTAL INTAKE WATER IN CC.	4700	3500	4300	3900	4500
TOTAL INTAKE SALT IN GM.	27	16	18	16	24

Special Notes on the Case :— Nothing particular.

thirst and a dry mouth are the important signs. In pure salt depletion the effect of salt loss resulting in water loss is mainly felt in the extracellular compartment, and hence symptoms of loss of osmotic pressure, hæmoconcentration, low blood pressure and of peripheral circulatory failure, predominate. In mixed salt and water loss symptoms of both the conditions develop. However, those due to pure water depletion predominate in the latter condition.

(5) Usually an ordinary uncomplicated patient requires about 3,000 cc. of fluid per day. This may be given as 2,500 cc. in the form of normal glucose solution (5 per cent) and the remaining 500 cc. as normal saline (0.9 per cent). Any excessive loss of fluid through vomiting, diarrhœa or sweating, must be added to this quantity, volume by volume, in the form of normal saline.

(6) Dangers of excessive water and salt ingestion in the immediate post-operative period are stressed. The salt ingestion should be restricted as far as possible in the period immediately following an operation, if there is not much abnormal loss from the body, because of natural retention of salt in the body in this period, thus avoiding the chances of developing œdema.

(7) Various common routes of fluid administration are discussed. Next to the oral, the rectal route is a very suitable convenient route for fluid administration. The danger of relying too much on the subcutaneous route for fluid administration has been emphasised. The intravenous route is the most suitable route if the other routes are not accessible and also in cases of emergency.

(8) An illustrative case report with the water and salt balance chart of the case is also given for a better understanding of the problem.

ACKNOWLEDGEMENT

I am much thankful to Dr. B. M. Bhardwaj, Medical Officer I/c O.P.D., Civil Hospital, Mandi, who helped me in many ways to complete this paper including figures.

REFERENCES

1. Bartlett *et al* quoted by Marriot (*vide* reference 6).

2. Coller, F. A., and Maddock W. G.: Water and Electrolyte Balance. Surg. Gynæ and Obst. **70** : 340-354, 1940.

3. Coller, F.A., Job V., Vaughan, H.H., Kadler, N.B., and Moyer, C.A..: Translocation of Fluid Produced by Intravenous Administration of Isotonic Salt Solutions in Man Post-operatively. Ann. Surg. : **122** : 663, 1945.

4. Fuge and Hogg, Quoted by Mason and Zintel.

5. Gamble James L.: Chemical Anatomy, Physiology and Pathology of Extracellular Fluid ; A Lecture Syllabus Ed. 5. Cambridge, Mass. Harvard University Press, 1947.

6. Marriot H.L.: Water and Salt Depletion, B. M. J. **1**: 245-250, 1947.

7. Marriot H. L.: Water and Salt Depletion, B. M. J. **1**: 285-290, 1947.

8. Mason R. L., and Zintel H. A.: Pre-operative and Post-operative Treatment page 136. 2nd Edition. Philadelphia and London, W. B. Saunders Co., 1945,

9. Rowntree quoted by Mason and Zintel (*vide* reference 8).

10. Streeten, D.H.P.: The Effects of Sodium and Chloride Lack on Intestinal Motility and Their Significance in Paralytic Ileus. Surg. Gynæ. and Obst. **91**: 421-434, 1950.

11. Van.Slyke, K. K. and Evans, E.I.: The Significance of Urine Chloride Determination in the Detection and Treatment of Dehydration with Salt Depletion, Ann. Surg., **128**: 129-391, 1948.

12. Webb, W. R., Lemmer, R.A., Elman, R.: Absorption Rates, Electrolyte and Volume Changes Following Subcutaneous and Intraperitoneal Injections of Solutions Containing Salt, Glucose and Amino Acids, Surg. Gynæ. and Obst. **91**: 265-270, 1950.

MEDICAL PROGRESS

RECENT TRENDS IN THE USE OF ANTIBIOTICS §

J. C. Patel *

Antibiotics are chemical substances produced by micro-organisms which have the capacity to inhibit the growth of bacteria and even to destroy them.[18] They are characterised by certain distinct physical, chemical and biological properties which make them ideal chemotherapeutic agents. They have a selective action upon different micro-organisms which may extend to genera species and even to some strains or individual cells. Some antibiotics act on gram-negative bacteria, some on gram-positive and some have action on both; others act on fungi, some of them are active also against rickettsiae and few on large viruses. A few antibiotics possess anti-protozoan activities.

They form a number of chemical compounds containing carbon, hydrogen and oxygen, e.g. penicillic acid. Some contain nitrogen in addition to the above e.g. streptomycin, gramicidin and tyrocidin. Others contain nitrogen and sulphur in addition to carbon, hydrogen and oxygen, e.g. penicillin. Compounds containing chlorine are chloramphenicol and aureomycin.

Some micro-organisms produce more than one antibiotic e.g. **Pseudomonas aeruginosa** form three separate compounds. Others prepare different antibiotics under different circumstances.

The same antibiotic might be produced by several different organisms e.g. various penicillins are formed by **P. notatum, P. chrysogenum, A. flavus, A. giganteus** and a number of other fungi. Similarly, streptomycin has been isolated from cultures of **S. griseus** and **S. bikiniensis.**

The nature of substrate may change or reduce the activity of an antibiotic e.g. serum or salts or serum proteins might neutralize the salt or inactivate the antibiotic. This explains the differences in action **in vitro** with **in vivo** of certain antibiotics. Aureomycin has adequate action **in vitro** against (S. typhi) but has very poor action in typhoid fever; though an antibiotic may have a marked action in animals it may have very little action in human beings. Hence antibiotics should be bio-assayed in human beings finally.

Some antibiotics like penicillin are readily destroyed by certain micro-organisms whereas streptomycin is highly resistant. Others are intermediate.

The antibiotics may act upon bacteria by interfering with the growth of bacteria and|or by interfering with the cell division or respiration or utilization of essential metabolites.

---

§ Based on a lecture delivered to Post Graduate Students Association, Bombay, March 1951

* Hon. Physician, King Edward Memorial Hospital, Bombay.

Many antibiotics are highly toxic e.g. actinomycin; whereas penicillin has no toxicity. Most of the antibiotics fall between these two extremes. The action of antibiotics upon various animal tissues also vary greatly.

A few antibiotics can be modified chemically so as to reduce their toxic properties e.g. dihydrostreptomycin.

Bacteria once sensitive to an antibiotic may gradually develop resistance to it when allowed to be in contact with it for some time. Resistance to streptomycin is developed rapidly while resistanc penicillin occurs very gradually. Reacquirement of sensitivity or loss of resistance may occur with some antibiotics and with some bacteria. The mode of reacquirement may be different.

The characteristics of an ideal antibiotic can be summarised as follows[18].

1. It should have a specific action on an organism and should not be a protoplasmic poison.
2. It should have a more potent action than a previously existing chemotherapeutic agent.
3. It must be active in the presence of body fluids.
4. It must not be destroyed by tissue enzymes.
5. It must not be toxic to the host, to individual cells, to a leukocyte, and tissues such as kidneys.
6. It should be stable and should be soluble in water or certain other readily available solvents.
7. It should not be excreted too rapidly from the animal body and should not accumulate to produce undesirable side effects.

Since 1945, more than a hundred antibiotics have been discovered, but not more than four or five have come into general use.

Antibiotics can be subdivided according to their source of origin.

1. **Anitbiotics produced by bacteria:** A large number of bacteria have a capacity of producing antibiotics. They are active on both grampositive and gram-negative bacteria and also on fungi, e.g. tyrothricin, polymyxin or aerosporin, bacitracin produced by B. subtilis, colicin produced by E. coli. These antibiotics have not come into general use because some of them are too toxic.
2. **Antibiotics produced by fungi:** Penicillin, clavacin, gliotoxin are examples.
3. **Anitbiotics of actinomycetes:** Streptomycin, streptothricin, chloramphenicol, aureomycin, neomycin, terramycin are examples.
4. **Antibiotic-like substances from plants (phytoncides):** Various green plants produce chemical compounds which have antibac-

terial properties. This work has been done largely in Soviet Russia, but otherwise it has not found wide application in chemotherapy. *Quinine* can be considered an example of this group.

5. **Antibiotic-like substances synthesised by animals:** Lysozyme found in saliva, in eggs, in tears; erythrin found in red blood cells, lactenin present in milk and active upon lactic acid bacteria are common examples.

We now consider antibiotics and their role in controlling the disease.

a. **Disease caused by gram-positive bacteria and certain gram-negative cocci:** Penicillin has extensive application in the treatment of diseases caused by these organisms. Bacitracin is highly efficient on some of these organisms.

b. **Disease caused by gram-negative bacteria:** These are resistant to penicillin but are sensitive to streptomycin, polymyxin, aureomycin, etc. Combination of two antibiotics may have a synergistic action on some organisms or might minimise the danger of rapid development of resistance. Streptomycin may be combined with sulfadiazine in combating some of the diseases caused by gram-positive organisms.

c. **Disease caused by mycobacteria:** Streptomycin is the best effective drug against this organism. Neomycin, aureomycin, streptothricin, and subtilin may have a slight action against this agent. The action of streptomycin can be supplemented by synergistic action of drugs like promin or other sulphones and para-amino-salicylic acid.

d. **Spirochaetal diseases:** Several antibiotics have effect upon diseases caused by these organisms. Penicillin is the most active and has superseded previous methods of treatment. Aureomycin and chloramphenicol may have slight but relatively ineffective action.

e. **Rickettsial Diseases:** Chloramphenicol, aureomycin and terramycin have effective action against the diseases caused by rickettsiae.

f. **Virus diseases:** Newer antibiotics have action against diseases caused by larger viruses such as psittacosis, lymphogranuloma and virus pneumonia. However, no antibiotics have been so far discovered which have any action against diseases caused by smaller viruses like that of common cold or poliomyelitis.

g. **Fungus diseases:** So far, we have not got any antibiotic which acts safely upon these diseases. Some antibiotics may have action 'in vitro' but are too toxic 'in vivo.' Penicillin has some action on the fungi-actinomycosis.

h. **Protozoan diseases:** Amoeba and plasmodium are affected by newer antibiotics like aureomycin, chloramphenicol and terramycin to a small extent. Antibiotics have found extensive application in the treatment of various animal diseases and also of some plant diseases.

PENICILLIN

During the course of the last two to three years, quite a lot of work has been done with a view to find out methods for prolonging the action of penicillin, of which these are now commonly used.

It is now recognised that if penicillin is given in a single large dose of 500,000 units, a detectable and therapeutically affective concentration persists in the blood for over 7½ hours.[6] Allowing for the factor that bacteria are known to take some hours to recover from exposure to penicillin to resume growth, an interval of 12 hours between two injections of such a dose is justified. In a higher concentration penicillin is actively bactericidal so it is often advantageous to start the treatment with 1 million units of penicillin. One million units of penicillin mixed with 25 cc. of glucose given intravenously in an acute infection like pneumonia brings down the temperature within 8-12 hours and the patient is often cured. It should be remembered that penicillin persists in the tissues a few hours longer even after it has disappeared from the blood. This is particularly true of diseased and necrotic tissues and this is the reason why penicillin, even in a smaller dose and at longer intervals, gives quite good results.[5]

The more recent method of prolonging the level is by giving procaine salt of penicillin. Procaine penicillin either in aqueous suspension or in oil fortified with crystalline penicillin is now very commonly used and these are very effective. If procaine penicillin is mixed with aluminium stearate (one per cent) and injected, the effective level is prolonged for a period of about 36 hours and 600,000 units of such a preparation has a prolonged action for four days. If 2 million units are given the action will be prolonged for a week. However, the last method is not commonly used in practice.

Procaine penicillin preparations have now become quite cheap compared to its predecessor Romanasky formula and from the economic point of view they are to be preferred. Procaine penicillin has also been used in the form of implants under subcutaneous tissue.[7,8] It is mixed with 20 per cent fat. 400 mg. implanted in the skin will produce effective concentration for a period of 14 days. One gram tablet of procaine penicillin will have effective concentration for a period of 23 days.

The third method of prolonging the action of penicillin is by delaying the excretion of the antibiotic by drugs like caronamide acting on tubules of the kidney. Benamide has similar action, is less toxic than caronamide. When caronamide is administered simultaneously with penicillin the concentration of the latter in blood is raised high and is useful in diseases caused by partially sensitive or partially resistant organisms. This method has been used successfully especially in cases of subacute bacterial endocarditis which often relapse after inadequate treatment and the causative organisms become partially insensitive.

Penicillin has a unique property that it will not have any further action beyond an optimum level for a particular micro-organism, and that is about 4 or 5 times the effective level. If the drug is in a higher concentration it is usually excreted unused. The action of penicillin is only evident on the organisms in a multiplying stage; that means that the disease should be active. If the disease and the causative organism is dormant, penicillin will be ineffective. That being so, the action of the drug depends on the stage and extent of the disease, i.e. the number of micro-organisms and the sensitivity of bacteria. This will explain why in diseases like cardiovascular syphilis where the disease is dormant, treatment with penicillin may have no effect.

Lately, a newer penicillin salt has been prepared. This is excreated in the lungs in ten times the amount present in the blood. The new penicillin, when injected, is found in far higher concentration in the lung tissue than in the blood than the average crystalline penicillin. This penicillin would probably be most useful in diseases of the lungs caused by penicillin-sensitive organisms. The effectiveness of penicillin when administered with iodine (orally or parenterally) is increased and so four or five times smaller doses of the antibiotic may be necessary to produce the effective action.[12]

STREPTOMYCIN

Streptomycin is now considered to be the most active drug in the treatment of tuberculosis in any form, either singly or in combination with para-amino-salicylic acid.[12] The present trend is to treat tuberculosis of the lungs with a combination of the two. In this way, resistance to the drug is minimised and delayed. The trend of dosage of streptomycin in the treatment of tuberculosis has undergone modification—1 gram daily or once in 3 days in a single injection may be given. Intermittent therapy of treating a patient for alternate weeks or months has no advantage; on the contrary, resistance of the organism to the drug might be increased. The question of the length of treatment with these drugs is still under trial, but it is found that the longer the treatment the more are the chances of the organisms becoming resistant.[4],[13] The toxic effect of the drugs *is less evident now that the dosage is lower.*

New sulphonamides have been developed during the World War II in Germany and results from that country are encouraging. The reports from American workers who have used both (sulphonamide and streptomycin) show that the latter is a far superior drug. The new sulphonamide (thiosemicarbazone) cannot replace streptomycin.

Streptomycin is still the most active drug for plague and diseases caused by **Pseudomonas pyocyaneus** and **Proteus vulgaris.** Because of the action of streptomycin on the 8th cranial nerve, it has been suggested for use in the treatment of Meniere's disease. Even though streptomycin might be active in a number of other organisms, its use will probably be confined to the treatment of tuberculosis alone, as a number of newer antibiotics are available with less toxicity and less chance of drug resistance i.e. in **B. coli** infection.

AUREOMYCIN

Aureomycin is a newer antibiotic with a very wide range of activity *and acting on a number of gram-positive and gram-negative* organisms and hence it would be a drug of choice in a number of conditions where different organisms might cause the same disease. Its action is bacteriostatic. Resistance to it has been known to occur. In lung infections like pneumonia it would be the drug of choice as it acts on pneumonias caused by streptococcus, staphylococcus, friedlander's bacillus, pneumococcus, hemophilus, virus pneumonia, psittacosis, and lymphogranuloma. Aureomycin is slightly less effective against the pneumococcus than penicillin, but when the organism is not known it would be practical to use aureomycin. It also has the advantage that it can be given by mouth in the patient's home. The disadvantage of this drug at present is that it is very expensive.

Aureomycin is useful in all rickettsial infections like typhus fever.

It is also effective in diseases caused by large viruses like virus pneumonia (primary atypical pneumonia), herpes simplex and zoster, psittacosis, and lymphogranuloma. It is also effective in **H. Influenzae** and influenzal meningitis, in brucella and salmonella, also in dysentery organisms. Aureomycin has been found to be effective in experimental plague infections and whooping cough. Even though effective **in vitro** against S. typhi it has not been found to be clinically effective in typhoid fever. In intestinal amoebiasis, aureomycin has been tried with success in 95% of cases but there is a high percentage of relapses. Aureomycin has partial action against malarial parasites particularly in animal experiments. But in human beings it has no justifiable claim.[3] Aureomycin has been tried in skin diseases like erythema multiformae and psychosis[16] with success. In trachoma, aureomycin used locally has been found to be useful, whether it is due to its action on secondary organisms or on causative virus is not known.

TERRAMYCIN

Terramycin, the newest of the broad-spectrum antibiotics, seems to have an assured therapeutic future. Clinical trials with terramycin over a wide variety of conditions have proved its efficacy in infections due to sensitive bacteria which are generally very similar to those of aureomycin with few exceptions. Aureomycin and terramycin appear to be practically equivalent alternatives.

CHLORAMPHENICOL

Even though chloramphenicol is similar to the last two drugs, it is much more commonly used in typhoid fever where it is the best available drug. Chloramphenicol, used in the early stage of typhoid fever, will reduce the incidence of two major complications, haemorrhage and perforation. Used at a later stage, it does not reduce the incidence or the mortality due to these complications. Chloramphenicol does not cure typhoid carriers. In the treatment of whooping cough some people consider chloramphenicol better than aureomycin. At the moment, it is certainly cheaper.

ORAL PENICILLIN[5]

Recently quite a few reports have been published about oral penicillin. The newer antibiotics—aureomycin, chloramphenicol and terramycin—are normally given by mouth and this is claimed as an advantage.

Penicillin is destroyed by acid in the stomach and there is also some loss in the upper part of the intestine. It is therefore necessary to give 5—10 times the intramuscular dose in order to achieve the same effect. The preparation absorbed varies in different subjects, but absorption is better on an empty stomach so oral penicillin should be given before meals. Antacids to overcome the gastric acid barrier have not been found helpful. Absorption is more constant in infants and young children and penicillin may be added to feeds. Here is the double advantage of avoiding injections and of reasonable economy, since the dose required is comparatively small on a body-weight basis. If, however, ten times the ordinary dose of penicillin is given, most patients absorb sufficient to combat the ordinary infections and, now that penicillin is plentiful and relatively cheap, there are occasions when oral penicillin might be an advantage.

Three grams of penicillin is equivalent to 5 million units and, if this amount of penicillin were given orally each day, there would be few individuals who would not absorb enough to deal with any ordinary infection. One would hesitate however, to use this method in a desperately ill patient in case the absorption was faulty or in patients with bacterial endocarditis or actinomycosis when very large doses may be required. The physician treating a disease responding to several antibiotics will have to decide on a number of points in selecting a drug: which antibiotic will be more effective, which more toxic, mode of administration and cost of administration.

Lately it has been found that there is some synergism or antagonism amongst the antibiotics or with some chemical substance like sulpha drugs.[1] Few examples may be quoted: there is synergism between penicillin and sulpha drugs against **Salmonella typhi**; between streptomycin and P.A.S. against tuberculosis; between streptomycin and sulpha drugs against brucellosis; between penicillin and streptomycin against **Streptococcus faecalis.** There is antagonism between penicillin and chloramphenicol against **Strep. pyogenes** in experimental animals. So, in the treatment of certain diseases, polytherapy with antibiotics may sometimes cause unintentional harm. This has been ascribed to the action of the newer antibiotics at a different stage of metabolism of bacteria. Penicillin is rapidly bactericidal only to multiplying bacteria. If another agent is introduced which inhibits multiplication its bactericidal action may be prevented. Penicillin and streptomycin are bactericidal whereas aureomycin and chloramphenicol have bacteriostatic action.

Antibiotics in amoebiasis: Bacitracin, aureomycin and terramycin have action against **Entamoeba histolytica.** The mode of action is not definitely known. Some people consider it might be due to the action of antibiotics on the accompanying bacterial flora. Bacitracin in the dosage of 80,000 units daily for a period of 5-10 days was found to be effective.

Antibiotics in the venereal diseases.[7]

Syphilis: Aureomycin[8] and chloramphenicol have feeble action on spirochaeta. Penicillin is still the most active antibiotic against this disease. Failure with one course of treatment implies more penicillin. Oral penicillin will be required in extravagant doses and is too risky for a serious disease like syphilis but it may be employed for weak babies with congenital syphilis. If the disease caused by spirochaeta is not active or if the organism is not multiplying, penicillin may not be effective. Penicillin may be used with other metals like arsenic and bismuth in the treatment of syphilis, but the recent trend is to treat syphilis in all stages with penicillin alone.

Gonorrhea: Penicillin is the most active drug. Streptomycin, aureomycin and chloramphenicol are effective in the order mentioned. It has been suggested that aureomycin and streptomycin, if used in the treatment of gonorrhea, may prevent masking of concomitant syphilitic infection.

Chancroid: Streptomycin is the only effective antibiotic against this infection; however, sulphonamides are more active than streptomycin.

Granuloma Inguinale: Streptomycin is the most active antibiotic, aureomycin and chloramphenicol being slightly inferior.

Lymphogranuloma venereum: Aureomycin and chloramphenicol are the active antibiotics against this disease, but sulphonamides are more active than antibiotics.

Non-specific urethritis: Streptomycin, aureomycin, terramycin and chloramphenicol will all be equally effective.

Oral penicillin tablets are now-a-days used in prophylaxis of venereal diseases instead of sulpha drugs.

Antibiotics in tuberculosis: The combination of para-amino-salicylic acid and streptomycin[13] is the most effective agent against this infection. Neomycin, aureomycin,[17] and chloramphenicol have no clinical value. Newer sulphonamides have some action.[14] The comparative value of streptomycin with newer sulphonamides is not yet assayed; but the results from America where both streptomycin and the newer sulphonamides have been used show that streptomycin is superior.

Rickettsial diseases: Aureomycin, chloramphenicol and terramycin are effective against the diseases caused by rickettsiae, and cost and availability will be the factors in choosing one out of them.

Protozoan diseases: Aureomycin and terramycin have action on **Entamoeba histolytica.** Bacitracin also has some action. Aureomycin has some action on malarial parasites but is not effective enough to be used in clinical practice.

Virus diseases: Aureomycin, chloramphenicol and terramycin have action on larger sized viruses, but no antibiotic has yet been discovered which has an action on a smaller virus like that of poliomyelitis.

Fungus diseases: Actimycin and streptothricin have action on diseases caused by them.

Search for newer drugs—antibiotics—a goal towards an ideal antibiotic continues. Let us hope it will be achieved in the near future.

REFERENCES

1. Annotation: "Antibiotic Synergism and Antagonism." B. M. J: 2: 1160, 1950.
2. Boger W. P. Flippin H.F. "Penicillin Plasma Concentration: Increase and Prolongation with Carinamide and Newer Depot Penicillin Preparations." J.A.M.A. 139: 1131-1136, 1949.
3. Cooper W.C., Coatney G.R. Imboden C.A. & Jeffery G.M.: "Aureomycin in Experimental Chesson Strain of Vivax Malaria." Proc. Soc. Exp. Biol. 72: 587-588, 1949.
4. Editorial: "Chemotherapy of Tuberculosis." B. M. J. 2: 1102, 1950.
5. Fleming Sir A: Modern Penicillin Therapy Practitioner, 165: 639-645. 1951.
6. Garrod L.P.: "Chemotherapy I, II, III & IV." B. M. J. 2: 453-456, 617-619, 669-671, 722-724. 1950.
7. Huidobro F., Croxatto R., and Luchini A.: "Prolongation of Penicillin Blood Level by "Implantation of Procaine Penicillin Tablets." Abst. of World Med. 8: 126-127, 1950.
8. Huidobro F., Croxatto R. and Luchini A.: "Prolongation of Penicillin blood level by Implanation of Procaine Penicillin Tablets." Proc. Soc. Exp. Biol. N.Y. 73: 201-2023, 1950.
9. Levidetti C. and Vaisman A.: "Aureomycin in the Treatment of Syphilis." Abst. of World Med. 8: 128-129, 1950.
10. Ling V. B.: "Plague." J.A.M.A. 144: 375-377, 1950.
11. Loza E: "Clinical Observation and Experimental Study of Combined Penicillin-iodine Treatment." Abst. of World Med. 8: 351-352, 1950.
12. Medical Research Council: "Treatment of Pulmonary Tuberculosis with Streptomycin and Para-amino-salicylic Acid." B. M. J. 2: 1073-1085, 1950.
13. Radenbach K.L.: "The Effect of TB I-698 and TB. IV on the Course of Tuberculosis Meningitis." Abst. of World Med. 549, 1950.
14. Robinson H.M.: "Aureomycin in the Treatment of Some Dermatosis," Arch. of Derma. Syph. 61: 384-396, 1950.
15. Robinson, H.M.: "Chloramphenicol in the Treatment of Chronic Discoid Lupus Erythematous." A Preliminary Report. J. Invest. Derm. 14: 309-311, 1950.
16. Steinbach, M.M., Dooneif, F.S. and Buchberg, A.S.: "The Use of Aureomycin in Pulmonary Tuberculosis." Amer, Rev. Tuberc. 59: 624-631, 1949.
17. Wakesman S.A.: "Origin and Nature of Antibiotics." Amer. J. Med. 7: 85-99, 1949.
18. Willock R.R.: "Orally Administered Antibiotics and the Venereal Diseases." Nature, 166: 466-1950.

DIABETES MELLITUS †

Bio-chemical Aspects

S. S. Ajgaonkar*

INTRODUCTION AND HISTORY

Diabetes Mellitus was known to Indian physicians over two thousand years back and its correct clinical descriptions were given by Charak,[1] Sushrut[10] and Wagbhat.[13] They knew that the urine is sweet in Diabetes and so they called the disease "Madhumeha" a disease with sweet urine. The English physician, Thomas Willis, of the 17th Century is given the credit by the Westerners for the first demonstration of the chemical nature of the disease who described the sweetness of the urine "as if there has been sugar and honey" in it. Dobson, in the 18th century demonstrated the presence of sugar in urine. In 1889 Von Mehring and Minkowasky, demonstrated on extirpation of the pancreas in dogs, that a condition like diabetes in man develops in the animal. Hyperglycemia, glycosuria and ketonuria appeared and when glucose was fed, it was excreted quantitatively in the urine. Since then chemical study of blood, urine and the study of metabolism of carbohydrates, proteins and fats has helped us to understand the disease in a better way.

The epoch making discovery of Banting and Best in 1923 of insulin—the internal secretion of pancreas, the proof that diabetes mellitus arises from intrinsic disease of the pancreas, was established. But recent studies suggest that diabetes mellitus may be more complex in origin and that the intrinsic disease of pancreas may not be the primary cause at all.

Experiments by Houssay,[2] Luckens[4] and others, demonstrated that pituitary and adrenal glands have an important role in the causation and maintenance of diabetes. Besides if a pancreactomy is performed in man, the diabetes which develops thereafter requires fewer units of insulin than the one which develops spontaneously and in whom the pancreas at autopsy may show only minor changes.

Diabetes therefore, seems to be a disease of metabolism due to imbalance of the endocrine glands. The disturbance develops in the hereditary predisposed individuals under the influence of factors which throw an excessive load upon endocrine glands' balance. Unlike the infectious diseases, it is not self limited and external influences except diet and infection have little effect on its progress. Unless endocrine imbalance is corrected it is difficult to control diabetes and a mere supply of insulin does not solve the problem as we see all the complications of diabetes such as arterio-scloresis, diabetic nephritis, diabetic retinitis, high blood pressure, etc., except coma, in cases treated with insulin.

---

†Paper read before the Bombay Medical Association on 2nd November, 1950.

*"Diabetic Clinic"—Sir Jamshedji Jeejeebhoy Hospital, Bombay.

Insulin of course prolongs the life of the diabetic much more so in juvenile cases where the prognosis was very grave in the pre-insulin era.

To understand diabetes, therefore, one must study its possible causation and its effect on the body and how it disturbs the body metabolism by changing the bio-chemical balance of the organism.

The human body is controlled by the endocrine glands, the anterior pituitary, adrenal, islets of Langerhans (pancreas), thyroid and gonads. These endocrines are also controlled by chemical agents like iodine in case of thyroid, sodium chloride in adrenal cortex etc. It is the chemical control which rules over our bodies, and so I am going to discuss the bio-chemical aspects of diabetes mellitus.

The cells of the body are surrounded by a circulating body of fluid containing solutes some of which pass in and out of the cells freely, others pass with difficulty. Apart from the nervous system the only means of communications between cells and organs is through the extra-cellular fluid and the introduction of chemical agents into the fluid is the means by which the chemical process within the cells may be profoundly modified.

The composition of the extra-cellular fluid is influenced by:—

(1) Physiological processes—digestion, ingestion of drugs etc.

(2) Pathological processes.

(3) Endocrine secretion—deficiency or increase which affect certain organs or tissues of the bodies.

The main function of the controlling mechanism of the body is to keep these changes within the limits in which cellular functions can continue. Food which we take is a mixture of proteins, fats and carbohydrates with vitamins and salts. The body organism forms all the compounds found in the living tissues largely by operation of synthetic process of diverse and complicated character. A brief consideration of the normal metabolism of these foods i.e. carbohydrates, fats, proteins and salts, may help us to understand the changes that occur in diabetes mellitus due to imbalance of the endocrine system.

NORMAL METABOLISM OF FOOD

1. **Carbohydrate metabolism:** The food which is taken as carbohydrates, i.e. cereals, sugar, fruits, tubers, and legumen are in the form of polysaccharides. The saliva, the gastric, duodenal and intestinal juices act on the same and convert the polysaccharides to monosaccharides, glucose or hexose, fructose and galactose and are absorbed in the small intestine; the portal vein carries these hexoses directly to the liver where a portion is stored in the polymerised form of glycogen. Glycogen in turn is converted to glucose when the body demands the same for energy. In this manner the blood sugar is kept at a relatively constant level at 80 to 110 mg. per cent. The monosaccharides glucose etc., are converted into lactic acid, CO_2 and H_2O. Some part of glucose is converted into fat—especially in animals such as the hog. The respiratory quotient in normal carbohydrate metabolism, is 1.0, while in diabetes mellitus, it is 0.71. or less.

2. **Proteins:** The proteins which are ingested usually in the form of meat, fish, egg, milk, etc., are acted upon by the gastric, pancreatic and intestinal juices and are broken down to its component amino-acids. They in turn are divided into glucose, non-protein nitrogen (ammonia and urea) and some are converted into body tissues; 58 per cent of the protein is converted into glucose.

3. **Fats:** Both animal and vegetable fats are ingested in the form of butter, ghee, cod liver oil, margarine and other vegetable oils. They are acted upon in the intestinal canal by bile, lipase and other enzymes and turned into fatty acids and glycerols. Glycerols are turned into carbohydrates. Thus 10 per cent of the fat which is metabolised as glycerols is turned into glucose. The rest, that is fatty acids, is converted into acetone and aceto-acetic-acid. These are termed "ketone bodies". The aceto-acetic-acid is normally oxidised to CO_2 and H_2O producing energy. The fats are deposited in various body tissues and organs as depots of energy which can be burnt at the times of emergency such as starvation, illness, etc.

The normal metabolism of carbohydrates, proteins, and fats has been described separately, for simplification, but in the human body these processes go on together. Carbohydrates are transformed into fats, amino-acids follow the pathway of carbohydrates and fats, possessing as well a special metabolism of their own. This interlocking of the metabolism of the major food stuffs has led to the confusion regarding the number of metabolic hormones that exist. But it must be understood that the endocrine glands do not operate as individual units whose functional levels are independent. Alteration in the function of one member is followed by an unbalanced operation of the others and by compensatory efforts on their part to readjust the normal state of equilibrium. The imbalance of compensatory effects following hyper and hypo-function of a single endocrine gland is apt to produce particularly if operative for a long period, a series of events that may completely obscure their original course. A great future lies in research in this field, for as soon as we can correctly interpret the symptomatology of human endocrine function, we will perhaps solve the problem of such diseases as diabetes mellitus, goitre, Addison's disease etc.

In the normal man, the proteins, carbohydrates and fats are utilised in the following way:—

1. Some portion, i.e. ¼ of the protein is utilised for the formation of the body protein for the wear and tear of the tissues and formation of different hormones, serum, albumin and globulin etc. The rest after de-amination, is converted into glucose and turned into liver glycogen and utilised as glucose whenever necessary.

2. The carbohydrate is turned into monosaccharides as glucose; the liver glycogen is again turned into glucose and its intermediary products. So both glycogen derived from protein and carbohydrate is converted into glucose and intermediatary products which burn as CO_2 and H_2O with production of energy.

THE DIABETIC METABOLISM

In the diabetic the metabolic defect lies in that the rate of combustion of carbohydrates is persistently incapable of acceleration to the maximum which it can attain in the normal subject. The defect may vary from the slightest impairment of this function, perceptible only when large amounts of carbohydrates are given to virtually complete the abolition of carbohydrate oxidation[5]. In this extreme state the respiratory quotient remains at or below 0.71 even after carbohydrate is given. Not only all exogenous carbohydrates, but all sugar from protein and other carbohydrate precursors is excreted as glucose in the urine. The ability to store glycogen is also lost in severe cases of diabetes as a response on the part of the liver to the unsatisfied demand of the tissues for the oxidation of carbohydrates. Similarly the ability to convert carbohydrates to fats is also lost.

This loss of ability to oxidise carbohydrates is usually due to imbalance of the endocrine system, causing deficiency of insulin, the internal secretion of pancreas. The deficiency may be due to:—

1. Lack of production of insulin by the pancreas which has less

islets of Langerhans or has been damaged by tumour, fibrosis, or degeneration etc., or the production of insulin may be inhibited by other factors. This is called absolute deficiency of insulin.

2. Relative deficiency of insulin. Though there is a normal secretion of insulin but anti-insulinogenic factors work against the insulin that is produced and put a portion of it out of commission.
3. Destruction or elimination is accelerated.
4. The access of insulin to the cells is blocked.

Insulin does not oxidise carbohydrates, it merely acts as an enzyme or facilitates the action of enzymes in the system that oxidised carbohydrates in the cells. So if there is any defect in the chain, diabetes may occur. This defect in the chain may explain the extrème resistance to the action of insulin displayed by certain diabetics.

We have noted above that in diabetes the glucose is not properly oxidised and utilised as energy with the formation of CO_2 and H_2O. The metabolism of carbohydrates from polysaccharides to monosaccharides is normal but it proceeds no further. Consequently, the blood is flooded with glucose and the blood sugar rises above its normal level of 80 to 110 mg. per cent not only that, it exceeds the normal kidney threshold of 180 mg. per cent and spills through the kidney in the urine. As there is no utilisation of glucose by the tissues they are starved of it and there is an extra demand on the liver for more glucose (glycolysis) which also causes flooding of the blood. It will be noted that there is practically no difference between the fasting glucose concentration in arterial and venous blood showing diminished glucose utilisation by tissues. So blood sugar examination is one of the important diagnostic methods in diabetes mellitus. The blood sugar at any time depends chiefly upon three factors.

1. The degree of impairment of the process of oxidisation of carbohydrates.
2. The vigor of the reactions to combat this defect.
3. The quantity of carbohydrate available, either exogenous and|or endogenous.

Lipid (Fat) Metabolism: As carbohydrate utilisation becomes progressively more impaired, the diabetic patient is increasingly more dependent upon fat as a source of energy. The resulting increase in the intermediary fat metabolism may be the cause of hyperlipemia. 100 cc of normal plasma contains 140 to 250 mg. of cholesterol, 190 to 450 mg. of total fatty acids and 370 mg. of neutral fat and 400 to 1400 mg. total lipids. In diabetes the blood fat may rise so markedly that the plasma assumes an opaque milky appearance.

If one examines the retinal vessels, the colour of the veins and arteries simulates salmon colour showing lipaemia. In diabetes the blood fat may rise so markedly that the total lipid concentration rises to 10 per cent of the plasma volume. Joslin considers blood cholesterol as a more reliable index of the fundamental clinical condition than is the blood sugar, which reflects a temporary state. A high blood cholesterol is a reliable evidence that diabetes is uncontrolled, its existence indicates that dangers are present or imminent and that immediate action to control the diabetic condition is imperative. He considers that cholesterol values above 400 mg. in a diabetic implies that serious complications exist or are imminent. So also cholesterol under 90 mg. per cent in a diabetic is undesirable, as that portends shortest duration of life after the test and the highest mortality[6].

Ketosis develops in spontaneous diabetes mellitus when the disturbance in carbohydrate metabolism becomes severe. It was thought that the appearance of ketosis in the blood and the urine was due to defective metabolism of the carbohydrate. Naunyn had expressed this as "The fats are burnt in the fire of carbohydrates" a dictum which is well known to every student of physiology. But recently it has been proved to be incorrect by biochemists like Stadie and others. They have proved by animal experiments that ketones—the intermediatory products of fat metabolism—are properly combusted by the body into CO_2 and H_2O and they are the source of energy in a total diabetic. The oxidation of carbohydrate is in no way essential for the utilisation of fats. The excess of ketone in blood and in urine is mainly due to excessive metabolism of fats which form the main source of energy. The ketones are formed to such an extent that the body is not in a position to utilise them and so there is ketonemia and ketonuria. The source of the fat is both exogenous and endogenous. The acetone bodies are formed mainly in the liver and are excreted through the kidney by way of urine, and through the lungs by expired air; that gives the typical smell to the breath of a diabetic patient. Expressed in acetones, the normal ketonemia is 1.5 to 2.5 mg. per cent. In severe diabetic acidosis this may rise to 50 mg. per cent or more. Normally, the total daily urinary ketone body excretion is less than 1 mg.; however, in unusually severe cases of acidosis, the daily urinary ketone excretion may exceed 100 mg. (Will the factors that accelerate the ketone utilisation solve the problem of diabetic nutrition?)

Except for increased tissue catabolism of the untreated diabetic, the metabolism of protein and other nitrogenous products is not characteristically influenced by diabetes as such.

Salt and Water metabolism—acidosis: As a result of foregoing events secondary distubances of fluid and electrolyte economy ensue. These disturbances may be the major factors in the production of coma and, its fatal outcome. The passages of large quantities of sugar, acertone, nitrogen products and electrolytes into urine provoke the exertion of tremendous quantities of water. Polyuria in diabetes may be so severe that in exceptional cases the daily urine volume exceeds 25 per cent of the total body weight. The specific gravity of the urine is usually high above 1030, because of the large quantities of glucose which are eliminated. Excessive diuresis is usually followed by some loss of total base especially if the ability of the kidney to produce ammonia is impaired. This, in combination with the increased formation of acid ketone bodies, accounts for acidosis. The word "acidosis" to describe the clinical condition was used by Naunyn in 1906 as a synonym to "ketosis". Acidosis is an abnormal condition caused by an accumulation in the body of acids or the loss from the body of alkalies. Van Slyke defined acidosis as reduction of blood bicarbonate, below the normal level, and suggested its measurement by use of CO_2 combining power of plasma—below 50 volume per cent. The degree of acidosis runs closely with the decreased CO_2 combining power of plasma. When the latter falls to less than 15 volume per cent (normal is 55 to 80 per cent) coma invariably ensues. The degree of hyperpnea or air hunger is proportional to the depression of CO combining power. A large fraction of acid ketone bodies is eliminated in the form of ammonia and fixed base salts. The continuous loss of fixed base thus incurred, entails a reduction of sodium and chloride concentration of the blood and tissues as well as a shift of hydrogen ion concentration of the blood towards the acid side. The polyuria and the base loss tend to cause hyponatremia and to a lesser extent hypochloræmia. It is noteworthy that since the reduction of base is equivalent to reduction of total electrolyte content in the body fluid it eventually leads to dehydration. As acidosis becomes more severe dyspnea and typical air hunger develop and coma marks the terminal stage. Another feature of the disturbed electrolyte metabolism of diabetic coma, which deserves more attention than it has received in the past, is the loss of large amounts of potassium from the body. Loeb Actchly and others have demonstrated a markedly negative balance for potassium as well as other basic ions during the development of diabetic acidosis and correspondingly large positive balance during recovery. Since most of the potassium of the body is in intracellular fluid, it is within the realm of possibility, that loss of potassium is responsible in part, for the disturbances of function of the cells which lead to the death in certain baffling instances of diabetic coma even if, in some cases, the electrolyte pattern of the blood plasma is restored to normal.[7]

I have till now dealt with the usual biochemical aspects of the diabetic which will help one to understand the principles of the treatment of the disease.

REFERENCES

1. Agniwesh: Charak Sanhita, Nidansthan, Ch. 4, Chikitsasthan, Ch. 6, 1st. Ed. Y. G. Dixit, Budhwar Peth, Poona, 1934.
2. Houssay B. A., Smyth F. S., Foglia V. G., and Houssay A. B.: 'Comparative Diabetogenic' Action of the Hypophysis from Various Animals, J. Exper. Med. 75: 93, 1942.
3. Joslin E. P : Treatment of Diabetes Mellitus, pg. 146-151 P. Lea and Febigar, Philadelphia, 1940.
4. Luckens and Dohan F. C.: Science, 92: 222, 1940.
5. Peters and Van Slyke: Quantitative Clinical Chemistry, Vol. 2. Williams and Wilkins, 2nd Ed.
6. Randell Sprague.: Diabetic Acidosis and Coma, Medical Clinics of North America, March 1947.
7. Scott and Fisher. J. Clin. Investigation, 17: 725, 1938.
8. Shohl. A. T.: Mineral Metabolism, Zinc, Pg. 246—247 1st Ed., Reinhold Publishing Corporation, New York, 1939.
9. Stadie W. C., Zapp J. A., Lukens F. D. W.: Effect of Insulin upon the Ketone Metabolism of Normal and Diabetic Cats. J. Biol. Chemi. 132: 423, 1940.
10. Sushrut: Sushrut Sanhita, Nidan-sthan, Ch. 6, Chikitsasthan, Ch. 11, 12, 13. 1st. Ed. Y. G. Dixit, Budhwar Peth, Poona 1934.
11. Tice F: Practice of Medicine, 1: 57, 1948.
12. Von Mering J., and Minkowaski O: Zentalbl. f. Klin. Med Id, 393, and Arch. Expper. Path. and Pharmc. 31: 83, 1893
13. Wagbhat: Ashtang-rhadaya, Nidansthan, Ch. 10, Y. G. Dixit, Budhwar Peth, Poona.
14. Young, F. G.: 'Permanent Experimental Diabetes Produced by Pituitary (Ant. Lobe) Injections, Lancet, 233: 372, 1937.
    'Growth' and Diabetogenic Action of Ant. Pituitary Preparation. B. M. J. 1: 715, 1944.
    "Growth" and Diabetes in Normal Animals Treated with Pituitary (Ant. Lobe) Diabetogenic Extract. Biochemical J. 39: 515, 1945.

ADDRESS TO FINAL YEAR STUDENTS

Dr. M. L. Gujral*

Sir Edward and Lady Mellanby, the Dean of the Faculty, Ladies and Gentlemen,

When I look back at the long line of illustrious teachers who addressed this gathering before me, and in other years, I am filled with a sense ot my own insufficiency. I have neither their stature nor their mature wisdom. What shall I therefore say to those of you who will leave this institution in another few months? What advice shall I give you, I, who have not garnered much wisdom myself?

The qualities admired in a practitioner of the healing art are many and diverse. First of all there is the question of a liberal general education. The students who enter the portals of this institution in their seventeenth year are woefully lacking in their knowledge both of the sciences and the humanities. Precious little they know of literature, history, philosophy or the social sciences. Their knowledge of medical chemistry and biology is most inadequate. An edifice raised on such foundations must of necessity be anything but satisfactory. What is more depressing is the lack of a liberal education not only among new entrants to the temple of Aesculapius, but also among those who have spent five long years in Medical Colleges, and practiced medicine for many more. No one can be a good physician whose reading is limited to what is written in medical texts alone. To my mind the preliminary education of a medical student needs careful thinking from seasoned educationists and only a Narendra Dev could discourse on it with profit.

After acquiring a sound preliminary education, it is of the highest importance for the student of medicine to gain proficiency both in basic and the clinical subjects. The young graduate when he leaves college must be fully conversant with the existing medical knowledge. This has made great strides during the past hundred years or more. The development of anatomy by Vesalius, physiology by Harvey, bacteriology by Louis Pasteur, and cellular pathology by Virchow has revolutionized modern medicine. "A physician is a man," said Voltaire, "who pours drugs of which he knows little into a body of which he knows less. "Voltaire, could not have said this if he were alive to-day and had witnessed the marvels of the antibiotic age. In the subject of pharmacology advances have been made during the last quarter of a century which exceed those in the preceding

---

*Professor of Pharmacology, Lucknow Medical College.

2500 years put together, and which are on par with those made in weapons of warfare. Man has now in his hands the power to overcome the harmful relationship microbial life can establish with him. The microbe is fighting a losing battle. Immense progress has been made in chemotherapy and the magic bullets which Ehrlich visualized in the beginning of this century are realities that any physician may use. New and useful knowledge has been gained in the fields of endocrinology, vitamins, preventive medicine and surgery. The importance of a regime and physical methods in therapy or what Swift described as Dr. Diet, Dr. Quiet and Dr. Merryman, is also fully appreciated. You must imbibe all this by a meticulous and a painstaking devotion to detail. And towards this end you should read your texts carefully, subscribe to a good monthly and a good weekly journal and also make a habit of buying a few special monographs every year.

Knowledge is important but by itself it is not enough. She has a twin sister, wisdom by name, whom you would do well to court. Keep a careful record of your cases. Observe closely. When you retire at night read up about your day's difficulties. This will help you to understand them and to develop in you a sapience and a penetration. There is a common belief among men that the more patients a doctor sees, the greater is his experience and the maturer his wisdom. Nothing is farther from truth than this belief. In some dispensaries in congested towns, some of our doctors dispose of hundreds of patients, sometimes as many as five hundred daily during the course of a few hours. In this curious country, Eye Melas are held at which hundreds of cataracts are operated upon in the course of a day or two. What prudence or profundity can such slip shod work gain for any one? Wisdom does not lie in numbers, it lies in the soundness of ones observations. The distinction between knowledge and wisdom was well drawn by the poet Cowper:

Knowledge and wisdom, far from being one,
Have oft times no connection. Knowledge dwells
in heads replete with thoughts of other men;
Wisdom in minds attentive to their own.
Knowledge is proud that he has learned so much;
Wisdom is humble that he knows no more.

Young Comrades, the profession to which you have elected to belong, is a most exacting one. It will require of you hard work. Work which will give you neither rest nor respite at least in the beginning. It will mean farewell to your evenings off, recreation, sports. leisure, club life or the remotest chance of a holiday. It will mean farewell to all these. It will steal your sleep. It will give you anxious moments when your patients refuse to get well or things go wrong. Your wives will nag for lack of attention. Your children will suffer from neglect. And were this all, it would not matter. For many of you it will mean a period or dry bread for years, and for the wives sweeping of floors and slaving in the kitchens.

To some the goddess of wealth may show a little indulgence after the first few years. But only on a few will she smile and that after long and arduous wooing. For practitioners of internal medicine and other specialities the task will be harder. The first ten years as a great physician put it, will yield bare bread, the second ten years bread and butter and the last ten, cakes and ale only to a few.

Those of you who have the capacity for hard work and perseverance will come out successful. Many will drag and dawdle and lose heart, and losing heart turn to other and less arduous ways of making money. Some will turn to trade, some try their luck at contracts and others, if the present conditions prevail, will hunt for permits and quotas which mean jam and no work.

Another high-ranking attribute in a physician is honesty. A successful physician, successful in the real sense of the word and not in its conventionally understood meaning—is above everything, honest. You should all cultivate this virtue. Prescribe few medicines, prescribe only those of which you know the action and prescribe them only when they are necessary. Do not order an injection that you can do without. Do not operate for the love of operating. A mistake of the head can be pardoned, not a mistake of the heart. More than 2,000 years ago said Plato in the Republic: "No physician, in so far as he is a physician, considers his own good in what he prescribes, but the good of his patients, for the true physician is also a ruler having the human body as a subject, and is not a mere money maker."

A good physician will also eschew, what Osler described as medical Chauvinism. Although there is enough room for proper pride of birth and place, jingoism or extravagant nationalism has been and continues to be the great curse of Mankind. The mad jingoists of Hitler's Germany brought to millions of human beings all over the world dissolution, devastation and destruction, unparalleled in the annals of history. And before the human race could have reasonable respite from the consequences of the past war, the jingoist vipers of Europe and America are active again and we stand on the brink of another cataclysm.

In this country nationalism and chauvinism have entered medicine as in no other country in the world. Medical Chauvinism in its worst form permeates not only the practitioners of Ayurveda but also the muddy mettled patriots. A system of medicine cannot be good simply because it is ancient and has its birth in this country. A system cannot be condemned only on the ground that it was born in parts remote and other than our own. The rest of the world did not reject the work of Laennec and of Louis Pasteur because it emanated from France, the work of Jenner Simpson, Lister and Flemming because they were British and of Virchow, Paul Ehrlich and Freud because they spoke the German language. Nor can you who live in this country afford to do so. The great discoveries of medicine as of science belong to mankind.

There is another aspect of Chauvinism which I would like you to consider. This abounds particularly in the centres where there is more than one Medical College, as in Bombay, Madras and Calcutta. Each institution tries to run down the other. An inter-university chauvinism is also not rare. The Madras graduate thinks he is the best in the country, the Lucknow graduate thinks that he is the best in Asia and the one from Bombay speaks disparagingly of both. This variety of Chauvinism also needs to be condemned but it must be distinguished from the loyalty to the Alma Mater and a healthy spirit of competition which are to be encouraged.

Chauvinism is a canker, a festering sore which is eating into the vitals of the corpus medicale in this country. And it cannot be eradicated unless all concerned agree to adopt a proper spirit of eclecticism, a willingness to take the good wherever found. The Ayurvedic physician must give up his medieval outlook and advance beyond the fourteenth century in which he is still living. He must reject what is valueless in his system and accept the great advances that have been made during the last one hundred years or more. The modern Indian physician on the other hand must also play his part. He should make an intensive study of the Ayurveda, examine things dispassionately, experiment and salvage whatever may be valuable. By doing so he will not only establish friendly relations with the Vaid but also do real service to science.

Youthful friends, before I conclude I would like to draw your attention to a great experiment.

The progress that has been made in the medical sciences during recent years, is phenomenal. It has put at our disposal agents which if used in the service of man, bid fair to make the psalmists three score years and ten. look as under estimate of the length of human life. The advances made in technology, however, have far outstripped those made in social organization. The fruit of the great discoveries is available at present only to a handful of rich and the bulk of mankind are still bereft of its benefit.

The experiment of socialized medicine which began in U.S.S.R. in the year 1917, has brought effective medical aid within the reach of all citizens of the Soviet Republic. The experiment has been extended to Countries of Eastern Europe and also to socialist England in which country medical aid is today available to all irrespective of the purse. Free medicine, free advice, free consultations from the specialists, free X-rays, free glasses and free dentures are available for everybody.

I would commend it to you to watch this experiment with care, to study it well and to determine when it can be introduced into this country. It may be in a decade, it may be introduced into this coun- country. It may be in a decade, it may be in two but ultimately it will have to be after suitable modification, applied in this country as well. It will also help the dry-bread doctor, and all doctors will get bread and butter. The cake and ale-doctor will probably oppose as he did in England and as he is doing in America today. But I have no doubt that his voice will be drowned in the stentorian thunder that your combined voices will produce. I urge you friends if you have the good of your country and of its teeming millions at heart to go ahead with this noble task, for as Emerson has said:

"Life is too short to waste,
In critic peep or cynic bark,
Quarrel or reprimand;
Up! Mind thine own aim, and
God speed the mark."

BOOK REVIEWS

Medicine for Students

By A. F. Golwalla, M.D., F.C.P.S. 684 pages, Price Rs. 16
Published by the author.

Dr. Golwalla's book 'Medicine for Students' is written in a telegraphic style. In the preface to the book Dr. Golwalla states that he has referred to a "host of text books, monograms, journals and pharmaceutical literature." The use of the word "host" in this context is rather unfortunate. It is never used for non-living objects. The word monogram means a figure consisting of several letters interwoven or written into one. It is a pity that an author embarking on writing a book should not know the difference between a monograph and a monogram.

There is a complete lack of a uniform plan in the writing of the book itself. Under most of the diseases, only the causes, the clinical features and the treatment are described. In a few instances, there are also definitions, complications, diagnosis and differential diagnosis. Pathogenesis, morbid anatomy and pathology are almost completely eschewed. Pathology seems to be to Dr. Golwalla what a red rag is to a bull.

The tropical diseases like malaria, typhoid, kala-azar etc., receive a most step-motherly treatment. And yet these are the diseases a practitioner in this country is called upon to treat almost every day during his professional career. The modern views on the pathogenesis of malaria receive only a passing reference. The indications for the use of the modern anti-malarial drugs are dismissed in a most sketchy manner. Under the treatment of typhoid fever, no mention is made of rest or the use of a bed pan, although rest is prescribed for most of the other febrile illnesses.

Brucellosis is said to be due only to ingestion of goat's milk and no mention is made of Br. abortus or Br. suis in the etiology of the disease.

The largest number of errors are, however, to be found in the sections on treatment. A long list of therapeutic measures is given for the student and the young practitioner to select from. There are no drugs of choice mentioned and no guiding hints given for the students who just pass their finals.

The long list of therapeutic measures, many of them of doubtful value, only succeed in making confusion worse confounded. The author himself has no notion of the dosage of some of the drugs he advocates. Under treatment of hypertension, veratrum viride is recommended to be used and the dosage mentioned is 1 tablet three times a day. A tablet may contain any amount of the drug from a fraction of mg. to a half Gram or more. The dose of nitrogen mustard to be injected intravenously is stated to be 5-10 Gm., for polycythemia vera on page 235, 0.1 mg. per Kg. body weight for leukemia on page 239 and 1 mg. per kg. body weight for Hodgkins' disease on page 241. Nitrogen mustards are dangerous drugs to employ and those who recommend their use should be fully conversant with their dosage and methods of administration.

Such mistakes could be multiplied a hundred fold if the whole book were to be examined critically.

Besides the errata at the end of the book there are many other typographical errors in the body of the book.

This is a dangerous book to get into the hands of the students and the practitioner.

M. L. Guzral.

Tumours of the Adrenal (Section VIII—Fascicle 29).

By Howard T. Karsner, M.D., Medical Research Advisor, Bureau of Medicine and Surgery, U. S. Navy, formerly Professor of Pathology, Western Reserve University. American Registry of Pathology, Armed Forces Institute of Pathology, Washington 25, D.C., U.S.A. Dol. 1.00*

Atlas of Tumour Pathology has been undertaken by the subcommittee on Oncology of the National Research Council, U. S. A. Tumours of the Adrenal is the second fascicle in the series of 39 to be published on tumours of various organs. The fascicles are printed in loose leaf form. This would facilitate binding in correct sequence. The first Atlas provides an index for the entire series. The text is restricted to pertinent current information and presentation of information is done in systematic manner. Preferred name and synonyms of each tumour are given together with a definition, gross and microscopical description and a selected bibliography.

The author divides the adrenal tumours into two main groups, the cortical and the medullary. Besides tumour-like lesions, Melanoma and secondary tumours are discussed and these add to the value and give a complete picture of the tumours of the adrenal gland. Diagram (Fig. 22) modified from Bisclshowsky to show development of cells of the sympathetic nervous system, helps in understanding the histogenesis of the tumours of the sympathetic nervous system.

The Atlas is well illustrated with photographs of patients, charts, photographs of specimens and photo-micrographs. Such pictorial presentation helps immensely in understanding the textual matter.

The Atlas is an indispensable guide and reference to the Pathologists and should get a hearty reception in our country.

*This and the subsequent Atlases could be brought by sending UNESCO Book Coupons. These could be purchased from Ministry of Education, New Delhi 3.

The request for the Atlases should be addressed to the Director of Registry, Armed Forces Institute of Pathology, 7th and Independence Avenue, Washington 25, D.C., U.S.A.

M. V. Sirsat.

CURRENT MEDICAL LITERATURE

MEDICINE

PRISCOL IN TREATMENT OF PERIPHERAL VASCULAR DISEASE.

Goodwin, J. F., and Kaplan, S.: B. M. J. 1: 1102-1107, 1951.
2 tables, 7 figures and 13 references.

Priscol has complex actions consisting of effects resembling the sympatheticomimetic amines, histamines and acetylcholine-like properties, and sympatholytic effects. In view of the lack of effective therapeutic agents for the ambulant treatment of patients with peripheral vascular disease, the authors decided to investigate the effects of oral priscol on 12 patients with occlusive vascular disease and 2 patients with Raynaud's disease. The dosage of priscol administered varied from 75-300 mg. a day by mouth for periods up to 3 months. The effect of priscol was assessed objectively by reflex heating tests and the measurement of circulation rate using sodium fluorescin. Subjective improvement of varying degrees was noticed in all except one case. Nine out of 10 patients with symptoms of intermittent claudication showed relief. In the two cases with Raynaud's disease the attacks were completely prevented by priscol. The toxic effects were slight. The authors concluded that priscol was of some value in the treatment of ambulant cases of occlusive disease, as an interim treatment in acute ischaemic cases, in patients with Raynaud's disease and in patients unsuitable for sympathectomy. Priscol is unlikely to replace sympathectomy. The ease of administration and the lack of serious toxic effects when given orally opens a field for further trials in occlusive vascular disease.

Eric Coelho.

CRUDE LIVER EXTRACT, REFINED LIVER EXTRACT AND FOLIC ACID IN THE TREATMENT OF PERNICIOUS ANAEMIA OF PREGNANCY,

Kothari B. V. and Bhende Y. M.: Ind. Jour. Med. Res. 38: 385-392, 1950. 1 table, 5 references.

18 patients with pernicious anaemia of pregnancy in Bombay were studied. 6 were treated with crude liver extract and 5 with refined liver extract, both given intramuscularly, and 7 with folic acid.

The dosage of the crude liver extract was 4 cc. on the first day, 2 cc. on the second day and thereafter 2 cc. every alternate day. The refined liver extract was given in 2 cc. on the first day, 2 cc. on the second day and 2 cc. every fourth day. Folic acid was given in the dosage of 15 mg. daily for the first ten days and 10 mg. daily thereafter. In some cases, folic acid was given by intramuscular injection in the dose of 15 mg.

They had equal success with crude and refined liver extracts. They consider refined liver extract better and more potent, the smaller dose required being an advantage. Folic acid, in their opinion, is the best of the three remdies, with advantages of oral administration and no side reactions. They also add that few cases may prove refractory to any remedy and the reasons for this are not fully understood.

J. C. Patel.

AN EXAMINATION OF A SUGGESTED LABORATORY METHOD OF ASSAY OF THE ANTI-PERNICIOUS ANAEMIA FRACTION OF LIVER EXTRACTS M. Parman R. M. and Underhill, S. W. F.: J. Pharm. Pharmacol. 3: 87-92, 1951.

Witts and his team had obtained macrocytic anaemia in rats by producing a blind loop of intestine in rats and had suggested that this method be used for standardising the liver extracts.

Authors using this method tested anahaemin liver extract in anaemias in such animals. The difficulties were (a) high (43 per cent) immediate post-operative mortality; (b) only 28 out of 104 animals developed anaemia within 2 to 3 weeks of operation, 22 of which recovered spontaneously; (c) 28 rats developed anaemia 6 to 45 weeks after operation; (d) The effect of anahaemin was not consistent and could not be repeated; (e) a reticulocyte response to anahaemin was observed both in controls and in operated rats.

The authors conclude that it is not a practicable method since it does not provide a reliable criterion of the potency of clinically active liver extract.

J. C. Patel.

RESPONSE OF MEGALOBLASTIC ANAEMIA OF PREGNANCY TO CRYSTALLINE PENICILLIN G, *Foy, H., Kandi A., and* Targreaves, A.: B. M. J. 1: 1108-1110, 1951. 11 references.

After the successful treatment of histamine-fast achlorhydric megaloblastic anaemia with crystalline penicillin G, the authors have used this substance in the megaloblastic anaemia of pregnancy without any other treatment and met with the same striking results. Crystalline penicillin G 4,000,000 units was administered intramuscularly daily for 17 days. The authors observed a maximum reticulocyte response within 5 to 8 days after the first injection. The expected red-cell count and haemoglobin level was attained on the fifteenth day. The patient was discharged with a red cell count of 4,300,000 and a haemoglobin level of 12 Gm. The response obtained in this case was similar to that following the administration of crude or refined liver, vitamin B12 or folic acid. The marrow reverted to the normal picture, the megaloblasts disappeared rapidly and the giant stab-cells more slowly. The authors are of the opinion that this response to penicillin may be due to any or all of the following: (1) Changes in the flora of the gut, which may lead to the destruction of antagonists or other factors interfering with the synthesis, absorption, or utilisation of haemopoietic factors; (2) interference with bacterial metabolism releasing haemopoietic factors for the use of the body; (3) an effect on protein metabolism and the synthesis of nucleo-proteins from basic amino-acids; (4) the presence of hitherto unknown haemopoietic factors; and (5) the destruction of toxins produced by bacteria.

Eric Coelho.

SURGERY

SURGICAL TREATMENT OF CEREBRAL PALSY, Caroll, R. E. and Craig, F.S.: Surgical Clinics of North America 31: 385-396, 1951.

Past experiences on individual problems has given valuable information to deal with these invalids.

(1) Upper Extremity:—

The following deformities appear in order of frequency:—

1. Flexion deformity of wrist.
2. Flexion deformity of elbow.
3. Adduction of thumb into palm.
4. Flexion of digits into palm.
5. Pronation of the forearm.

Criteria for treatment:—

The hardest task of spastic patients is, the proper evaluation of deformity, which may need repeated assessments. The patient must cooperate in the recovery process after operation. He must know how to use his newly acquired correction, otherwise, no benefit. He should also realise that the extremity will not regain absolute normality, and more than one surgical intervention may be required.

The younger the patient better the results.

Technic of treatment:—

Fusion of wrist: Very good for flexion deformity of wrist. Fusion is planned between the distal radius and the distal, row of carpal bones. When the digital flexors are powerfully deforming, the base of metacarpals 2-4 are included in the fusion. If the wrist flexors are tight, they are severed. Plaster immobilization for 16 weeks is given. This method cannot be used until radial epiphysis has stopped growing. It is useful both in spastic patients and those with an athetoid component.

Fusion of Ulna To Radius:— Expose the distal third of radius and ulna, and strip the interosseus membrane and pronator quadratus. Rotation of the firearm is made to the desired position. This forces the ulna against the radius where a notch has been made to receive it. Put a Kirshner wire through both bones in the forearm and immobilise in plaster for 12 weeks. This operation corrects the rotation deformity of the forearm, when other means are not possible.

Fusion of Metacarpophalangeal joint to thumb:— Arthrodesis of this joint aids in stabilising the function of an opposing part. It is frequently used along with tenotomy of deforming muscles or tendon transplantation.

Bone block for stabilising thumb:— It permits improved function, when tenotomies or transplants fail to bring the thumb out of palm. A wedge of iliac bone is placed between first and second metacarpals, and held by wires, followed by plastering.

Transplantation of Flexor Carpi Ulnaris into Extensor Carpi Radialis Longus:— It gives very good results if the patient is young and intelligent, it corrects a flexion pronation and ulna deviation deformity. The flexor ulnaris is divided proximal to the pisiform bone at the wrist is retracted up, passed subcutaneously across the dorsum of forearm and inserted into the tendon of ext. carpi radialis longus, in full supination of forearm with full wrist extension, followed with 4 weeks plastering. When the tendency of ulna deviation persists, ext. carpi ulnaris is transplanted into ext. carpi radialis brevis, as a secondary procedure.

Tenotomy:— Care must be taken to prevent reversal of deformity by dividing the deforming pull. Division of adductor of thumb at its insertion can release a serious deformity. Similarly, section of flexor sublimis tendon in the midpalmer area releases flexion deformity of single digits.

Nerve Section:— It is an extensive but valuable method, but it is better to deal with the tendon. The authors do not commend the posterior root resection and sympathectomy in the upper extremity.

Correction of Flexion deformity of elbow:— The authors have accepted this deformity, as it does not limit the function.

(2) The Lower Extremity

The authors are certain that surgery is of no value in the rigidities, ataxias, or tremors and of limited use in athetosis.

The Foot:— Deformities due to contracted muscles must be corrected before braces are prescribed. The technic is described.

Tendon transplants and divisions in the foot:— Division of the posterior tibial tendon is most useful in equinovarus foot followed or preceded by stretching of the deformity in plaster. A short leg brace limiting plantar flexion is worn, with passive home stretching of calf. With a varus foot, the ant. tibial tendon may be transplanted to cuboid, by the technique described, followed by plastering. Better results are obtained after gastrocnemius neurectomy and division of post, tibial tendon. If the valgus deformity is due to an overactive peroneus longus, this tendon is divided and attached to navicular. Post. tibial tendon is not divided, but a gastrocnemius neurectomy may be done.

Gastroenemius neurectomy:—Indications are:—1. Recurrence of equinus contracture after stretching in plaster. 2 Continued weakness of ant. tibial due to a strong calf. 3. With dorsiflexor transplants. The technique is described.

(3) The Knee:—

The treatment of genu recurvatum is with a stop lock brace, and mild contractures are dealt with manual passive stretching.

Severe contractures:— Plaster stretching of the knee alone is unsatisfactory, and should be combined with posterior capsulotomy, and hamstring neurectomy is valuable for recurrence.

The Hip:— For hip flexion contracture, divide fascia lata and all the intramuscular septa of the anteroir hip region, and extend the leg, cutting any tight structures as discovered, including add. longus. If adduction be a problem, resect the ant. obturator nerve. Increased abduction is obtained by release of tensor fascia femoris and suturing it to gluteus medius tendon of origin. Long leg plastering is done with knee extended to 180 degrees.

Fractures in Cerebral palsy:— The authors agree with rigid internal fixation with plate and screws, both in cases of femur, tibia and fibula.

Arora.

USE OF VARIOUS PLASTIC CATHETERS IN THE SUBARACHNOID AND PERIDURAL SPACES, Davidson, H. H. et al: Arch. Surg. 62: 540-547, 1951. 3 figures, 2 tables.

The first continuous conduction nerve block anaesthesia through an indwelling catheter was instituted by Eugene Abruel in 1930, where a fine silk elastic catheter was introduced just anterior to the lumbo-aortic plexus through a 14 cm. needle.

Love in 1935 used an indwelling ureteral catheter for continuous drainage in meningitis. This technique was then modified for use for continuous caudal anaesthesia. The authors in 1946 started this technique substituting the polyethylene and vinylite (B-D vinyl tubing) plastic catheters for the costlier, larger and more traumatic shellacked nylon uretheral catheters, for continuous caudal, continuous peridural and continuous spinal analgesia and anaesthesia, and utilised these techniques in obstetrics, surgery and therapeutics in more than 1,900 cases.

The polyethylene catheter has been used in the majority of cases. It has the great advantages of being flexible, relatively inelastic but will stretch markedly without breaking. It is inexpensive and is discarded after use. It is introduced through a 17 gauge needle and admits a 25 gauge hypodermic needle. It must be prepared for use by chemical sterilization (1:1000 zephran chloride) for 24 hours.

The B-D vinyl tubing is slightly less flexible and may be sterilized by autoclaving, and though of smaller diameter has a larger lumen.

The shellacked nylon ureteral catheter has occasionally been used with its wire stilet when less flexibility is required.

Each batch of catheter material is tested for irritative properties by inserting a small segment in the anterior chamber of a rabbit's eye for 7 days.

The plastic catheter is non-irritating and does not limit the patients movement and has been used for the administration of peridural and subarachnoid saline for severe post-spinal headache, for the administration of local anaesthetics and analgesics and in the treatment of tuberculous meningitis for the repeated administration of streptomycin. Complications were encountered only in two cases, in one a cellulitis superficial to the sacrum rapidly responded to chemotherapy in the other an aseptic mild meningitis followed the introduction of the catheter which disappeared without sequelae.

Eustace J. de Souza

PEDIATRICS

NEPHROTIC SYNDROME, EFFECT OF ADRENOCORTICOTROPHIC HORMONE, Riley, C.M.: Pediatrics 7: 457-571, 1951.

The author records his observations on 14 cases with the nephrotic syndrome while under the following short term treatment with adrenocortico-trophic hormone (ACTH-Armour). All 14 cases were under 16 years of age, most of them between 2 to 5 years. They all showed the classical findings of the nephrotic syndrome: anasarca, hypoproteinemia, massive proteinuria and hyper-cholesterinemia; in these cases, no distinction was made between 'pure nephrosis' and 'nephrotic phase of nephritis'. ACTH was administered by the intramuscular route every 6 hours for 4 to 6 day 'courses'; the individual dose was usually 15 mg. (60 mg. day), larger children receiving higher doses.

The facts presented show too much variation to permit any interpretation of the action of ACTH in the nephrotic syndrome. Five patients given eight courses showed complete clearing of edema in seven instances, one failing to show any response to a second course. Four patients given six courses showed significant but incomplete clearing of edema each time. Five patients showed no clinically significant response to seven courses. Post-treatment studies varied from 7 to 15 months. Some of the patients have remained symptom-free, others had relapsed several times, but responded to subsequent periods of treatment; still others after early successes had failed to respond to later ACTH administration. *In only one case* had a permanent remission taken place. The author considers that at best, the use of the hormone appears to offer a means of controlling the edema of the nephrotic syndrome.

F. A. Nazareth.

TERRAMYCIN HYDROCHLORIDE IN THE TREATMENT OF SALMONELLA CHOLERAESUIS BACTEREMIA, Scott, R.B. and Wooding, C.H.: Pediatrics 7: 349-353, 1951.

In children, S. **choleraesuis, (suipestifer)** infection produces three types of disturbances: a typhoid-like fever, an acute gastroenteritis and a bacteremia (septicaemia). Infection occurs through eating contaminated foods but may be also transmitted through handling of infected animals; the incubation period varies from a few hours to several days. Predominating symptoms are either enteric, pulmonic or septic, and include headache, *nausea, vomiting, fever, diarrhoea, meningismus and occasional* splenic enlargement; leucopenia or leucocytosis may occur. Diagnosis is bacteriologic and consists of isolation of the organism from the blood, urine, stool or pus and demonstration of increased agglutination titer in the serum. Complications due to septic localization include arthritis, meningitis and abscesses; bronchitis and bronchopneumonia may also occur. The duration of the disease is variable, but usually shorter than typhoid fever; its treatment has hitherto been unsatisfactory.

The authors describe 3 cases of S. **choleraesuis** bacteremia successfully treated with oral terramycin. All these children aged 2, 2 and 4 years had positive blood cultures on admission, stool cultures were negative. The first child received 2 Gm. of terramycin daily for 3 days and then 3 Gm. daily for a further 7 days; the other two, 3 Gm. daily for 14 and 15 days respectively. In the latter two cases, blood cultures were negative within 48 hours; in the first case blood culture was positive on the 5th day of treatment, but four subsequent daily cultures were negative. In all three cases, the toxicity passed off and the temperature was normal within 5 days of therapy. No untoward reactions were observed. The authors believe that terramycin is superior to sulphonamides and other currently available antibiotics in the treatment of S. choleraesuis bacteremia in children.

F. A. Nazareth.

PULMONOCARDIAC FAILURE, O'Connell, W.F. and Lee, Y. C.: Pediatrics 7: 394-399. 1951.

The syndrome of pulmonocardiac failure (also called scoliotic or kyphoscoliotic heart) is a distinct clinical entity, in which patients with scvere thoracic and|or spinal deformities eventually succumb to heart failure brought about by prolonged respiratory insufficiency. These patients have cardiac and respiratory embarrassment resulting from a deformity of the spine and|or thorax, which cause a decrease in volume and in expansion of the thoracic cage. In order of importance, the casual factors are poliomyelitis, congenital or hereditary defects, rickets and tuberculosis. The deformity, occasionally present from birth, usually develops during childhood, achieving its maximum effect when the patient attains full growth; death occurs after the age of 30 years. The outstanding symptom is dyspnea, usually present for many years; the patient may carry on moderately restricted activity until the sudden appearance of severe paroxysmal dyspnea, nocturnal dyspnea, weakness, palpitation or fainting mark the onset of pulmonocardiac failure. On examination, the patients are small, frail and dyspneic with predominant abdominal breathing. Tachycardia may be found with occasional elevation of diastolic pressure and rales, as the only sign of congestive heart failure, though peripheral edema may occur; in the late stages, severe respiratory distress and cyanosis may be present. Cardiac enlargement is difficult to evaluate, the ECG may show right axis deviation; the other laboratory studies are normal. Autopsy shows right ventricular hypertrophy, the presence of the deformity, and beyond emphysema, atelectasis or edema a complete absence of any significant abnormality in the pulmonary vascular tree, either gross or microscopic. The sequence of events leading to death seems to be: (1) a decrease in respiratory capacity, (2) an increase in pulmonary resistance and pulmonary arterial pressure acting for a long time, and (3) right ventricular hypertrophy and dilatation with eventual cardiac and respiratory failure.

The authors report a case with many of the above findings, but with some unusual features. A boy aged 10 years, had thoracic deformity, dyspnea, cyanotic attacks and terminal cardiac failure. Autopsy revealed the typical findings. Unusual features were: (1) the presence of marked congenital spine an rib deformities with anomaly of diaphragmatic attachment and (2) the presence of dyspnea almost from birth with death at 10 years in contrast to survival to 30 years or more.

F. A. Nazareth.

CONGENITAL TRACHEO-ESOPHAGAL FISTULA WITHOUT ESOPHAGAL ATRESIA, Helmsworth, J.A. and Pryles, C.V.: J. Ped. 38: 610-617. 1951.

The authors discuss the symptoms, signs and treatment of this rare variety of tracheo-esophagal fistula and report a case of their own.

According to the authors, paroxysms of coughing precipitated by feeding are the first diagnostic feature; coughing, sometimes followed by vomiting, begins shortly after swallowing and is more severe when the food is less viscid, solid foods being swallowed with negligible difficulty; the cough disappears when the child is fed by gavage. The second diagnostic feature is gaseous distention of the gastro-intestinal tract; rapid, direct inflation of the stomach during coughing is pathognomonic of fistula between the tracheo-bronchial tree and the upper alimentary tract; coughing or forced expiration is believed to shunt part of the air from the trachea into the esophagus. Pneumonitis, the third diagnostic feature, is caused by recurrent aspiration of oesophagal contents and results in frequent visits to the physician; it is interesting that the pneumonia most frequently affects the right upper lobe. Iodized oil in the esophagus will pass through a tracheo-esophagal fistula more readily if the patient is prone than if he is upright or supine; failure to visualize a fistula by this method does not exclude the possibility of its existence. Endoscopic examination of the esophagus and the trachea must be done in every case as it may locate the exact level of the fistula; bronchoscopy may show liquids bubbling through the ostium from the esophagus, or, the tracheal opening of the fistula may be delinated after methylene blue has been given orally. Preoperatively, the patient is given fluids, electrolytes, whole blood and its derivatives; efforts are made to maintain a clear oropharynx and keep the trachea free of oral and esophagal secretions; feeding is preferably by gavage; these last two procedures will lower the incidence of pneumonia, which if present however, is treated by antibiotics. The operation consists of a right extrapleural or transpleural approach to the mediastinum and closure of the fistula, the lung is then gradually reexpanded. Postoperatively nutrition is maintained by gavage until contrast visualization of the esophagus is done on the sixth day, thence fluids are given by mouth if no abnormality is found, and four days later, the child is given the appropriate diet for its age.

In the case reported, from the symptoms and signs, the authors diagnosed tracheo-esophagal fistula without esophagal atresia in a six month old boy on his third admission to the hospital, although no fistula could be demonstrated roentgenographically or on bronchoscopy at that time: two previous admissions failed to reveal any abnormality. Operation confirmed the diagnosis, the fistula was closed and the patient discharged on the twelfth postoperative day. At 13 months the patient looked healthy and weighed 26 pounds (birth weight 7 pounds 13 oz.) Four roentgenograms are reproduced, two before, and two after operation.

F. A. Nazareth.

METHYLENE BLUE IN THE TREATMENT OF METHEMOGLOBINEMIA IN PREMATURE INFANTS CAUSED BY MARKING INK:

Etteldorf, J.N. J. Ped. 38: 24-27 1951.

Among other causes, methemoglobinemia may occur in premature and full-term infants from the use of diapers stamped with aniline-containing ink. Drabkin ascertains the methemoglobin content of the normal erythrocyte to be 0.5 per cent or less of the total pigment, and that a minimum of 1.5 Gm. per cent must be present in the peripheral blood for visible cyanosis to occur.

The author reviews the literature on methemoglobinemia, and records his results of treating with methylene blue 8 premature Negro children who developed this condition from diapers stamped with ink containing aniline. These infants suddenly became listless, refused feeds and became dusky in color with visible cyanosis of the mucous membranes and nail beds; the cardiac and respiratory systems were normal. Their incubators had an intense odor of aniline suggesting that absorption of aniline may also have occurred from the respiratory tract as also by way of the skin from the diapers which were marked by ink containing aniline. They were all given 1.5 mg. of methylene blue per kilogram of body weight as a 0.1 per cent solution in the scalp vein. The results were dramatic, cyanosis disappeared within 20 minutes; thereafter the course was uneventful and the children made continuous weight gains not unlike those observed prior to the poisoning.

F. A. Nazareth.

HYPOTHYROIDISM IN CHILDHOOD, Braid, F: B.M.J. 1: 1169-1176-1951.

Thyroid deficiencies in childhood are most common and most amenable to treatment.

Nomenclature and Aetiology: The word 'cretinism' is used loosely to refer to all types of hypothyroidism in children. Endemic cretinism is the product of generation of goitrous families. The cause of sporadic cretinism is less definite, the children are the off-spring of healthy parents. Probably sporadic cases are due to developmental defect, either the gland being absent or small

Acute infections in the mother during pregnancy like influenza may lead to inflammatory changes and fibrosis of the foetal thyroid. Postnatal infection may also be a cause e.g. measles and pneumonia. The use of thiouracil in the treatment of hyperthyroidism increases the danger of congenital goitre as the drug can pass through the placenta and be excreted in the milk, but the changes are reversible and the infant recovers spontaneously if breast feeding is avoided.

Diagnosis:— Diagnosis depends primarily on the appearance of the patient and the change which takes place after giving thyroid extract. Diagnosis is confirmed by X'ray examination for signs of delay in skeletal development (delay in ossification), cholesterol (high) and phosphatase (low) level in the blood and electrocardiogram. Improvement after thyroid medication is revealed in these indices as well as in the general appearance, and periodic examinations are useful for assessing progress and adequacy of treatment.

Congenital Hypothyroidism is due to development defect of the thyroid gland or where the gland has been damaged in utero as a result of some maternal infection. The foetal thyroid becomes active at about the 3rd month. There is a two-way transfer of thyroid hormone through the placenta. The myxoedematous mother of a normal baby looses her signs of myxoedema during pregnancy, and an infant with no thyroid may be quite well developed at birth and show signs of deficiency only after several weeks. Most cases come under observation between the 6th and 12th month and the importance of recognising the condition during the time of most rapid growth of brain and body cannot be over emphasised.

The commonest complaint before the age of 4 months is that the baby has become slow in feeding and is becoming more lethargic. In spite of the low intake of food, the weight increases and the quiet, fat baby with yellowish pallor suggesting anaemia that does not respond to iron, is suffering from thyroid deficiency. Umbilical hernia or abdominal distension or constipation may be present. The usually dry, cool skin, protruding tongue.

dull, sad expression, hoarse voice and myxoedematous firmness of the tissues which gives a peculiar stiffness of the limbs, gradually appear, making the full picture of the 9-12 months old toothless cretin. The retarded mental and physical development becomes quite apparent.

Post-infective hypothyroidism: The development progresses normally for some time and symptoms date from some acute infective illness such as whooping cough or pneumonia. Hypothyroidism is not striking in this group as in the previous, but delayed skeletal development, open anterior fontanelle, inadequate number of teeth and supra-clavicular pads are apparent. The child is short for his age, physically inactive and does not show normal zest in play. It may be mentally dull.

Endemic cretinism: They come under observation late, never before the age of two years; history is vague, the child has never been very active nor does it display interest in his surroundings, teeth have been cut late, learns to walk late and to talk still later. His voice is gruff, the sounds produced may be inarticulate, myxoedema not pronounced but there is considerable stunting of growth. Goitre may be present or may develop later. Dwarfish, goitre and poor response to thyroid are accepted characteristics of endemic cretinism. The brain damage is probably a part of the general degenerative state and cases may also be associated with a damage of parathyroid.

The first group is the most important, for on early recognition and adequate treatment during the period of most active growth of the brain, the child's future largely depends. The second group is readily recognised. The third group is the least satisfactory for the treatment.

Clinical features: The thyroid hormone is responsible for the normal development of all tissues but when it is deficient the various tissues are not affected equally nor are the corresponding systems in different patients.

Skeletal system: Roentgen examination of the skeleton reveals arrested growth shown by increased density of the provisional zone of calcification and the delay in appearance of ossification centres. The influence of thyroid on growth of bone is shown in a few weeks, and the appearance of fresh centres of ossification within a few months. In deficiency, instead of a single centre gradually spreading outwards to include the whole, multiple islets appear; these gradually coalesce and produce a fragmented appearance, instead of one of uniform density, to which the term 'epiphysial dysgenesis' has been given, which is most marked in the head of the femur and femoral neck, resulting in a waddling type of gait.

Muscular atony is common though not constant, resembling pseudohypertrophic muscular dystrophy.

Alimentary Tract: Lack of appetite, slowness of feeding, constipation, meteorism are present. Inadequate treatment results in a chronic type of diarrhoea which clears up when the dose of thyroid is suitably increased. In spite of adequate treatment, constipation associated with megacolon may occur.

Blood: Anaemia is usually present but not severe and bears no relation to other signs: A fall in haemoglobin and red cells sometimes occurs during early treatment. This is due to restoration of the plasma volume. The reticulocyte response to thyroid is a useful point in diagnosis.

Heart: Electrocardiogram shows a characteristic change from the normal.

Biochemical findings:

Cholesterol: A level of above 116 mg.|100 cc. is a confirmatory evidence of hypothyroidism, but it may be within normal limits. The cholesterol will fall after a single dose of thyroid in a normal child but will return to normal quickly. In hypothyroidism, the fall will last for several weeks.

Phosphatase: A low phosphatase level is common but not always.

Treatment and its Control: Infants suffering from deficiency of thyroid hormone are particularly sensitive to its administration and the initial dose should be low. The swelling of subcutaneous tissues presenting a generalised non-pitting oedema and localised supra-clavicular and, more rarely, axillary pads, is due to an extracellular accumulation of mucoprotein which exerts sufficient osmotic pressure to withdraw fluid from plasma to the extracellular spaces. Thyroid treatment dissipates the mucoprotein and the associated fluid is excreted. There is rapid disappearance of supraclavicular pads and loss of weight due to fluid loss. In incautious dosage, the loss of both extracellular and intracellular fluid may be so great that the infant may become dehydrated. A daily dose of 1|8 gr. of the extract or ¼ gr. on alternate days is safe and it should be increased by that amount at intervals of 4-5 days. As a result of therapy, the infant feeds more willingly, temperature becomes normal, the colour improves and facial expression changes.

Signs of too high dosage are a sudden rise in temperature, an increased frequency of stools and further loss of weight. If such signs occur, thyroid should be stopped for 2-3 days and restarted at a slightly lower level. A safeguard against overdosage: Omit the dose on one day in each week.

L. Banerji.

VENEREAL

AUREOMYCIN AND ITS EFFECT IN EARLY SYPHILIS. Roderiques, J. E. et al: Arch of Derm. & Syph: 63: 433-439, 1951. 3 Tables and 4 Figures.

In order to evaluate aureomycin in syphilis the authors treated 67 patients (3 sero-negative primary, 2 sero-positive primary, 62 sero-positive secondary) of syphilis with aureomycin as per following treatment. Schedule: initial oral dose of 2 Gm; another 2 Gm after 4 hours and thereafter 1 Gm every 4 hours day and night until a total of 70 Gm had been administered in 11 1|3 days. Surface spirochetes were rid of in an average time of 39 hours. All lesions involuted completely but the open lesions of syphilis healed little later with aureomycin than with trivalent arsenical or penicillin.

The cumulative percentages of treatment results, as determined by the six to seven month observation period, for 62 patients with secondary syphilis were as follows:— 59.7 per cent, sero-negativity; 21.1 per cent., 3 Kahn units or below; 15.8 per cent, 4 Kahn units or more; 1.7 per cent, reinfection, and 1.7 per cent, relapse. Comparing these results with those obtained by 2,500,000 units to 3,400,000 units of penicillin (for the same observation period) no significant difference in effect was noted except for high seronegativity (about 7 per cent) obtained with penicillin. Failure rate with penicillin was 12.2 per cent and that with aureomycin 19.2 per cent.

High and sustained blood levels of aureomycin were easily maintained by the oral route.

Cerebrospinal fluid aureomycin levels were not detected after a single 2 Gm. oral dose but were present in 50 per cent of patients during the multiple oral dose schedule. No serious reactions were noted.

Most patients had nausea and vomiting which were minimised by preliminary administration of aluminium hydroxide gel and 25 per cent glucose solution by mouth. A Felix Herxheimer reaction occurred in 17.9 per cent of cases. Preliminary results of this study present evidence that aureomycin is effective in the treatment of syphilis. The authors conclude with a suggestion that continued studies are necessary to determine its effectiveness after longer periods of observation and its position with the therapeutic armamentarium against syphilis.

T. K. Mehta.

RESULTS OF PENICILLIN THERAPY FOR NEUROSYPHILIS AT BELLEVUE HOSPITAL, Dattner, B., et al: 32: 33-39, 1911. 4 tables.

During the last six years well over 600 patients having some form of neurosyphilis were seen by the authors. Of these only those who had active neurosyphilis were treated with one or the other form of penicillin treatment alone. Diagnosis of active neurosyphilis rests on spinal fluid findings viz pleocytosis in addition to other laboratory evidence of neurosyphilis. Of the 438 patients treated with penicillin alone for various types of active neurosyphilis, 400 became inactive and remained inactive for periods varying from 6 to 75 months.

The various preparations of penicillin used were aqueous solutions of sodium penicillin, penicillin in oil and beeswax, and procaine penicillin in oil and aluminium monostearate. With aqueous solution of sodium penicillin the routine treatment was 40,000, units every 3 hours for 150 doses (i.e. about 19 days). When P O B was used treatment consisted of from 10 to 15 daily injections of 600,000 units and most of the patients treated with procaine. Penicillin in oil and aluminium monostearate received 15 daily injections of 600,000 units (total 9 million units). Because of its relative freedom from reactions and its excellent therapeutic effect, procaine penicillin in oil and aluminium monostearate is now preferred for the treatment of all types of neurosyphilis in the above dosage schedule.

As stated above there were 38 failures as judged from the effect on spinal fluid. 31 were retreated. Out of 31, 25 were retreated once, 3 twice, and another 3 thrice. The dosage varied from 6 million units to 30 million units depending on failure rate and previous treatment. Of 31 retreated, 27 attained inactivity of the spinal fluid. It must be noted that because clinical improvement cannot be expected when signs and symptoms are due to irreparable damage in the central nervous system the evaluation of treatment in the above series is based entirely on spinal fluid examination made every 3 or 4 months, the first year after treatment and at 6 months intervals thereafter. Unfortunately authors have not mentioned specifically normal figures for various spinal fluid findings accepted by them for the study.

T. K. Mehta.

DERMATOLOGY

CONGENITAL ABNORMALITIES OF THE SKIN, Brain, R.T.: Practitioner: 166: 480-487, 1951.

A variety of lesions, many of which may be present at birth whilst others become manifest in childhood or may even be delayed to adolescence, are considered under congenital abnormalities of the skin. The following are some of the anomalies in order of frequency of occurrence: nevi, xeroderma and ichthyosis, epidermolysis bullosa, xeroderma pigmentosa. The following ones usually develop about puberty or in the next decade: epithelioma adenoides cystecum, leiomyomas, adenoma sebaceum. Finally the author has considered some conditions which, according to some, arise from developmental abnormalities. They are: urticaria pigmentosa, xanthomas, and pseudo-xanthoma elasticum.

The author has discussed in short, the main clinical features of diagnostic value and treatment of all the above conditions. It will be interesting and informative to refer to some of them. Nevi or birth marks constitute the largest number of congenital abnormalities of the skin. They are vascular and non-vascular. The former includes capillary nevi (or hemangioma), cavernous nevi, spider nevus, lymphangiomas etc. Whilst the latter includes various pigmented and nonpigmented moles warty nevi also called nevus unius lateris and ichthyosis hystrix. The spider nevus is best treated by coagulating the central vessel with a fine galvano-cautery or diathermy needle. In capillary nevi the prognosis worsens with the depth of the colour, the port-wine mark usually resisting every kind of treatment although the intensity of the colour may be considerably reduced. Some of the pale birth marks may disappear spontaneously. These superficial blemishes may be treated by carbon dioxide snow pencil for 20 to 60 seconds, repeating the application after two or three months by which time the inflammatory reaction provoked, will have subsided. Large irregular areas are more suitably treated by brushing on a slush made by a little acetone to the powdered Co2 snow. Two or three quick applications are enough to produce a satisfactory reaction. The snow treatment being painful, alternatively thorium X radioactive paint is also recommended in the strength of 1500 electro static units per cc. of varnish. Cleanse the discoloured area with alcohol or ether and apply the paint. The risk of scarring is negligible as the radioactivity of thorium X depends on alpha particles which have little power of penetration. Thorium X may be applied monthly for 20 to 30 paintings and, if a satisfactory response is to be expected, considerable paling should be noted after 12 applications.

Cavernous nevi practically always disappear spontaneously in the course of a few years and therefore are rarely found in adults. Nothing need be done for lesions on covered areas but it is the custom to treat those on the face and other exposed parts of the body with small doses of X-rays, say 200 to 300 r, at two to three monthly intervals. The latter lesions respond well to short exposures to half strength unscreened radium plagues, which provide a convenient source of beta rays. Deeper lesions may be injected with thrombosing agents such as a 10 per cent solution of sodium chloride, or a few minims (one or two) of tincture iodine or of dilute hydrochloric acid. Only a minim or two of the latter two agents should be injected deeply into several parts of the swelling, or necrosis or ulceration is likely to occur. It may be taken as a general rule that if a vascular nevus calls for treatment, the sooner that treatment is applied the more effective it will be.

As regards pigmented nevi or moles, excision with plastic surgery is the best treatment for smaller lesions, but if they are extensive nothing can be done. A malignant melanoma rarely arises in a widely spread hairy mole, but a small, smooth, darkly pigmented mole is probably best treated by a wide excision within the first two decades, or immediately upon any active growth being observed.

Xeroderma pigmentosa is a condition in which the child's skin is intolerant of ultraviolet light. The first exposure to bright sunlight may be followed by an acute actinic dermatitis. There is no curative treatment, therefore protective measures are the best line of defence. Skin may be protected from ultraviolet light by applications of 10 per cent tannic acid in 50 per cent spirit, or by opaque calamine lotion. On dry skin yellow soft paraffin is also useful. Quinine or para-amino-benzoic acid are not recommended by the author.

T. K. Mehta.

POLYTHIONIC ACID IN THE THERAPY OF ACNE VULGARIS AND SEBORRHOEIC DERMATITIS: Clark, W., Finnerud and Murray-Riddel J.: Arch. of Dermat, and Syph. 63: 373-375, 1951.

3 tables and 10 references.

After making a passing reference to the multiplicity of therapeutic measures employed for acne vulgaris, the authors single out sulfur as the most effective remedy.

In view of the prominent position occupied by sulfur in the therapy of acne, a preparation of sulfur known as dermasulf (polythionic acid preparation) was utilized in the treatment of both acne vulgaris and seborrhoeic dermatitis. Dermasulf is a stabilized solution of complex polythionic acids of the general formula $H_2 S_{10} O_6$. It is colourless and odourless. Since the polythionates are water soluble they penetrate the skin more easily and to a greater extent than elemental sulfur. Sulfur in this form is more effective than in polysulfides, which are easily oxidized, precipitating elemental sulfur. The polythionate solution presumably delivers the complex sulfur solutions within the affected skin.

Method of application: 2½ per cent to 5 per cent dermasulf was applied morning and night for about 23 months on an average in both diseases. Majority tolerated 5 per cent solution.

Results: Of 141 cases of acne vulgaris, 90 were benefited, while 50 remained the same and one became worse. Therapy was well tolerated. A few, however, got irritation with 5 per cent solution.

Of 112 cases of seborrhoeic dermatitis, 80 were benefited (92 were scalp cases).

Dermasulf was thus found to be an effective anti-acne and anti-seborrhoeic agent and as good as any other similar remedy minus their disadvantages e.g. colour, odour, deposit, etc.

T. K. Mehta.

SUBCUTANEOUS INJECTIONS OF PROCAINE PENICILLIN IN TREATMENT OF CHRONIC SYCOSIS VULGARIS AND HYDRADENITIS SUPPURATIVA AXILLARIS: Belson, M.A.: Arch. of Derm. and Syph., 63: 380-382, 1951.

The pathology in the above two chronic pyogenic diseases is deep to the skin right down to the subcutaneous tissue. Therefore to be effective, any therapeutic agent must attack the casual pathogenic organisms at this site in sufficient concentration, amount and form for continued effect. It is a wonder that even topical application and intramuscular injections of penicillin were many times ineffective in these conditions.

Acting on the above hypothesis, the author first used aqueous penicillin G (Potassium) subcutaneously at the site of infection. But attendant pain precluded further trial with this form of penicillin. A change to 300,000 units procaine penicillin per cc in water mitigated pain but blocked the needle. Next a combination of procaine penicillin (300,000 units per cc.) and hyaluronidase enzyme (the so-called spreading factor) proved very sucessful. Finally, the author could inject procaine penicillin successfully without the hyaluronidase if 150,000 units of Penicillin per cc. of distilled water and a 22 gauge needle was used.

Injections were given only in chronic plaques. Each area was treated separately. Injections were repeated every 2 or 3 weeks and only from one to four injections were required to get satisfactory results.

The above treatment was tried successfully in 8 cases of sycosis vulgaris (all 4 to 5 years duration) and 23 cases of hydradenitis (of several years duration). Clinical results were remarkable. There were no systemic, local or sensitivity reactions to any of the ingredients. The method fulfils the objects in view viz. a repository drug at the proper site in adequate concentration. Finally the author also recommends the procedure for chronic infections of a similar nature.

T. K. Mehta.

TUBERCULOSIS VERRUCOSA TREATED WITH STREPTOMYCIN: Kern, A. B., Arch. of Derm. & Syph. 63: 378-380, 1951.

On reviewing literature, the author could find only two cases of tuberculosis verrucosa cutis treated with streptomycin. He reports a third case of his own.

Report of the case:—A 35 year old female patient had pulmonary tuberculosis with positive sputum. She also had verrucous tuberculous lesions on her left hand for four years, not responding to any local treatment. A biopsy confirmed the diagnosis of tuberculosis verrucosa cutis. As in previous cases, patient was given streptomycin in a dosage of 1 Gm. daily for six weeks. Response of cutaneous lesions was striking; at the end of 2 months, with the exception of slight erythema, there was complete involution. Three months later erythema also disappeared. Despite the dramatic effect on the skin condition streptomycin produced no change in pulmonary disease as shown by X-ray and positive sputum.

Formerly X-ray, Co2 snow and surgical excision were the only treatment for this condition. The above results indicate that streptomycin is one more mode of treatment.

The author points out that one of the serious limitations to the use of streptomycin in the treatment of tuberculosis is the development of resistance of the tubercle bacilli to the drug. This may occur as early as the thirty-fifth day when low doses are employed and even sooner when larger doses are used. Therefore it is suggested that if there is evidence of tuberculosis elsewhere in the patient, consultation with a phthisiologist is advisable before such therapy of cutaneous lesion is instituted and if given, low doses (not more than 1 Gm. per day) over a short period (not longer than 5 to 6 weeks) should be employed.

T. K. Mehta.

RESIN OF PODOPHYLLUM IN TREATMENT OF MOLLUSCUM CONTAGIOSUM; Sherwood, W., Barefoot and Greensboro N. C.: Arch. of Dermat. and Syph. 63: 256-259, 1951|

It is not always possible to resort to destructive measures for treating molluscum lesions which are often too many and in patients who are non-cooperative because of pain caused by the procedure. For such cases the authors advise topical applications of 20 per cent resin of podophyllum in 95 per cent alcohol.

The authors have given a detailed report of a successfully treated case and make mention of two more. The treatment is simple, safe and effective without causing any discomfort or sequelae. It took about 4 months for complete disappearance of lesions in the first case on weekly application of the resin paint. In subsequent cases the paint was applied on alternative days and the period of healing was reduced to about a month or so.

T. K. Mehta.

DERMATITIS HERPETIFORMIS IN AN INFANT, Evants, D.R.: Brit: J. of Derm. 61: 89-94, 1949.

After reporting the disease in an infant in detail the author makes the following observations:

(1) Criteria for diagnosis:— (i) Inveterate bullous eruption. (ii) Well-being of the child. (iii) Blood eosinophilia. (iv) Positive iodide patch test. (v) Notable improvement with arsenic.

(2) Variations from certain features of adult disease: e.g. itching, multiformity of eruption, grouping of lesions and pigmentation are not necessarily found in children.

T. K. Mehta.

INDETERMINATE LEPROSY, A NEW CLINICAL VARIETY, Findlay, G. H., Brit. J. Derm. 63: 100-104, 1951.

Leprosy was always discussed under the definite types—lepromatous and tuberculoid. These polar types stand at two extremes of the scale. One often encounters atypical cases and they are grouped as indeterminate cases in the new classifications discussed at the Havana Conference in 1948.

There are numerous cases which will fall in this indeterminate type or simple macular type of Cairo conference. But the following case which the author came across belonged to this type and was unique in the sense that there was no record of a similar case in the available literature.

The author saw a female patient aged 24 years. She had lepromatous lesions on forehead, nose, cheeks and ears and had swelling of legs, feet, forearms, hands and a recent ulcer on left shin. These lesions were lepromatous in all respects—clinical, bacteriological, immunological and histopathological. After about a year of these lesions a second rash consisting of papules and annular rings appeared in the trunk and the arms. The rash was symmetrical and was distributed in inverse relation to the lepromatous infiltrate. There was no anesthesia over the lesions, no bacilli could be seen and the lepromin test was negative. Histopathology suggested a lepromatous picture in deep cutis near the subcutaneous layer and the picture gradually turned to that of a tuberculoid type as one traced it towards the epidermis.

Discussing the case the author points out that transitions of one polar type to another have largely been considered in terms of a change from the tuberculoid to the lepromatous, and hardly ever the opposite. What is most interesting about the present case is something which cannot be brought out by any scheme of classification. This is the existence in one patient of two different types of leprosy, each practically sparing the territory of the other.

Γ. K. Mehta

NUTRITION

THE ENERGY METABOLISM OF MAN DURING OVERFEEDING, Munro, H.N.: Brit. Jour Nutr 4: 316, 1950.

Effect of excess feeding on nitrogen retention and energy metabolism of an healthy individual are described. Not much data is available on this point though there is information about studies with malnourished people. Three previous reports in connection with overfeeding are mentioned. The significance of increased B.M.R. recorded therein is, however, according to the author, doubtful.

The subject of the present study is of 20 years age, 61 Kg. body weight and height 166 cm. Four overfeeding experiments are described. After receiving adequate basal diet providing 12.1 Gm. nitrogen and 2850 calories for a period of eight days, extra energy was supplied in the form of (i) raw milk, (ii) boiled milk, (iii) meat with lactose and butter or (iv) soyabean with lactose and butter respectively in the four experiments. Each of these provided about 680 calories.

Four figures are given each representing changes in body weight, R.Q., B.M.R. and N balance, for the different extra diets fed, covering the basal period, overfeeding period of eight days and a period of basal diet for three days to which the subject is then transferred.

As a result of this surfeit feeding, marked increase in body weight and in N retention were noticed. This is attributed to excess energy intake and not to the increased protein intake, which by itself causes only a temporary rise in N balance. No increase is noticed in R.Q. and B.M.R. during overfeeding. On the other hand, sometimes a lowered B. M. R. up to 30 calories|sqm.|hr. is recorded. Changes in surface area due to increase in body weight did not exceed 1 per cent.

No correlation between N retention and B.M R. for a particular day was observed during surfeit feeding. The author was thus unable to find a relationship between N retention and energy metabolism. After discussing the relationship between these two under other conditions reported in literature previously and in the light of his observations, he concludes that the association between protein metabolism and B. M. R. appears to be of a superficial nature.

M. V. Patwardhan.

THE EFFECT OF GROWTH AND DEVELOPMENT ON THE COMPOSITION OF MAMMALS, Spray, C. M. and Widdowson, E. M.: Brit. Jour. Nutr. 4: 432, 1950.

The mammals selected for this study are mice, rat, rabbit, pig and cat. Their body chemical composition is reported over a period extending from birth to the end of suckling period. In some cases study is carried through maturity. In rats and rabbits the analysis for males and females are reported separately. The composition of different constituents as water, proteins, fat and minerals as Na, K, Ca, Mg, P, Zn, and Cu is given graphically. Most of the results are on fat-free basis.

In each case birth was followed by an increase in fat percentage with a corresponding though not equal decrease in water content. With rat and rabbit the fall in the latter was greater than the rise in fat. In both these animals the females contained more fat than males.

Protein increased gradually. More increase took place during suckling period and thereafter it became slow until it reached a steady concentration of 21—24.5 per cent.

At birth in all these species there was more sodium than potassium in the body. K increased and the former decreased until both reached a constant level when K concentration was about twice that of Na.

At birth the rat and rabbit were found to have a low Ca content 300—350 mg. and 480 mg.|100 Gm. respectively. During suckling period a large increase took place, after which the values tended to be constant being characteristic of maturity. In pig, however, which was born with high Ca level (about 1 Gm.|100 Gm. body weight), the value fell during suckling period, after which it increased and again there was a fall from weaning period after 112 days.

Phosphorus increased with Ca. The Ca: P ratios throughout growth are also recorded. The final values were the same for all species, i.e., about 1.7—1.8.

The adult animals in all species contained about the same amount of Mg, 45 mg.|100 Gm. body weight.

There appeared a fall during suckling period in the iron content, after which the values again rose. In case of rat and rabbit the Fe content was higher in females than in males, the difference being mainly due to the content of extra hepatic tissue. Studying the effect of iron supplements to pigs during suckling period, the authors noted no change in the inorganic constituents and the protein percentage only increased.

The difference in zinc in the various animals was attributed to its presence in appreciable quantities in epidermal structures. The cat, that is born with hair on the body, was found to have maximum Zn at birth. A considerable increase in zinc took place in early stages in case of rat and rabbit, followed by a fall. In case of pig and cat there was very little change from birth to maturity. In all species the zinc content of liver decreased after weaning.

After a rise during suckling period, copper concentration also fell after weaning and in all cases in adult the amount was found to be approximately 0.2 mg.|100 Gm. body weight.

A table is included at the end, which compares chemical composition of the adults studied with that of man.

All the constituents of the body do not appear to attain a steady level at the same time when one constituent is found to reach constancy the others are still increasing or some are already stable. Thus no time could be fixed as a particular period of chemical maturity when all the components are supposed to reach a steady level.

Comparing the approximate age at which puberty sets in, in different species, with the appearance of chemical maturity, the authors found that the pig did not reach a mature composition until after puberty while the cat was chemically mature long before.

In the light of the above findings the authors suggest that further study as regards this idea of chemical maturity is necessary before it is widely applied.

M. V. Patwardhan

THE EFFECT OF HEAT TREATMENT ON THE NUTRITIONAL VALUE OF SOME VEGETABLE OILS, Crampton, E.W., Farmer, F. and Barryhill, F.M.: J. Nutr. 43: 431, 1951.

Thermal polymerisation conducted in an atmosphere of inert gas is a method used sometimes in processing edible oils (as herring oil). This renders them less susceptible to exposure to heat and light. The paper describes the effects of such heat treatment on the nutritive value of oils as linseed, rapeseed, corn, peanut, soyabean and herring oil.

The oils were heated in a salt bath at 275oC for varying lengths of time in the presence of a current of carbon-dioxide. These were then incorporated in the basal diet of young growing rats at 10 per cent or 20 per cent level. The effect is assessed by recording the growth rate, the food consumption and the general condition of health and comparing with the controls. Animals fed on these treated oils, excreted dark, sticky faeces and showed oily matted coats.

The authors found that heat polymerisation lowered the nutritive value of oils, which was also influenced by the degree of unsaturation and the period of heat treatment of the particular oil. A toxic resulting factor in the oil appears, according to them to be responsible for their lowered nutritive value. In a later communication, the authors (E. W. Crampton et al—Jour. Nutr. 43, 533, 1951) have ruled out the possibility of vitamin E deficiency causing the retardation of growth. Vitamin E is likely to be destroyed in the heat treatment of the oils. They also observed that peroxidation of polymerised linseed oil was not responsible for the development of any toxic factor.

M. V. Patwardhan.

SOME PHYSIOLOGICAL EFFECTS OF SALT RESTRICTION IN THE RAT,

Danford, H. C., and Herrin, R.C. Am. J. Physiol 165: 128, 1951.

Three groups of male albino rats with average weights of 45, 65 and 160 Gm. respectively were subjected to dietary restriction of sodium chloride and|or potassium chloride. Diet deficient in sodium chloride lowered the ascorbic acid content of the adrenals, progressing for a period of 60 days over which the observations were carried out. In 65 Gm. rats, however, there was no significant reduction by the end of 4, 30 and 45 days. There was a relative increase in the weights of adrenals and kidneys. The weights of thymus and spleen decreased. The changes appear to be influenced by the age, the younger ones being more susceptible. The authors conclude that NaCl deficiency led to stimulation of the adrenal cortex with increased secretion of 11—17—oxycorticosterone. The failure, however, to lower the percentage of lymphocytes or eosinophils indicates that the increased secretion was of desoxycorticosterone type.

The diet deficient in KCl produced the same variations except that there was lymphopenia and eosinopenia, which denotes stimulation of the adrenals by adrenocorticotrophic hormone and the cortex secreting the 11—17—oxycorticosterone hormones.

The possibility of inanition interfering in the results was ruled out by paired feeding.

M. V. Patwardhan.

THE ACTIVITY OF GLUTAMINASE IN THE HUMAN PLACENTA,

Luschinsky. H. L.: Arch. Biochem and Biophysics, 31: 132, 1951.

A method for the assay of glutaminase activity in the human placenta is described. Optimum conditions of the procedure are discussed. This enzyme whose optimum pH lies at 9.0 was found to be activated by phosphate. Values are obtained covering the whole period of pregnancy. The data is divided into four groups according to the period of gestation, early pregnancy, mid-trimester, late pregnancy and term pregnancy. The mode of termination did not affect the values. The glutaminase activity is found to decrease towards the end of pregnancy to about one-third of its value in early pregnancy. The possibility of this reduction being due to decreased cellular activity is ruled out by calculating the ratio of total N|dry weight which did not change.

The author suggests that the glutaminase activity may provide ammonia to serve as a base sparer or for amino acid synthesis. It may also liberate glutamic acid for transamination and N transfer in urea synthesis. The other possibility mentioned by him is the provision of α ketoglutaric acid as a respiratory substrate.

M. V. Patwardhan.

Indian Journal of Medical Sciences
(INCORPORATING THE MEDICAL BULLETIN)

VOLUME 5 OCTOBER 1951 NUMBER 10

COPYRIGHT BY THE INDIAN JOURNAL OF MEDICAL SCIENCES

ORIGINAL ARTICLE

PULMONARY SUPPURATION

K. L. Wig *

Due to marked advances in radiology during the last two decades, and almost astounding advances in chest surgery during the recent years and especially since the diagnosis of pulmonary tuberculosis has been properly clarified and placed on a very sound footing, more and more attention is being paid to the problems of pulmonary suppuration.

In this paper I intend to present an analysis of 69 cases out of which 28 were diagnosed as lung abscess, 22 were proved to have bronchiectasis and 19 were considered to be suffering from the cystic diseases of the lung.

The number of the latter category is surprising even to me for the condition has always been considered to be rather a rare one.

LUNG ABSCESS

We will take up the lung abscess first. Most of the patients were poor, living on insufficient diet. Out of 28 cases, 23 were males and 5 females. This discrepancy amongst the sexes is almost surprising. The ages were distributed as follows :—

Below the age of 14 years	3
Between 15 and 25 years	3
Between 26 and 40 years	6
Between 41 and 60 years	14
Above 60 years	2

Out of the 28 cases, 9 visited the hospital in an acute stage, *i.e.*, within an arbitrary period of 6 weeks, while 19 came in the chronic stage.

For the sake of brevity, I am omitting any description of symptoms and clinical features, etc., of these cases, and I come straight to the radiological appearances.

---

* Professor of Medicine, Medical College, Amritsar.

Roentgenographic Findings—This, obviously, is the most important investigation for the purposes of diagnosis, localisation, proper treatment and for finding the progress of a case. In this connection it must be stressed that lateral roentgenograms along with A. P. ones are absolutely essential if proper localisation and if proper treatment is to be instituted. As regards our cases a cavity was visible in every case. This may be because we have not included but rejected for the purpose of this paper, cases of suppurative pneumonitis where no cavity was visible, as otherwise some doubtful cases will come in and so would vitiate any analysis. I must, however, mention that many such cases do exist. Brock[3] considers them to be 50 per cent of all cases of lung abscess.

The edges of the cavity were found very irregular and coarsely ragged in one case which was in all probability a necrosed and infected peripheral carcinoma. In four cases, masses in the cavity could be detected in plain roentgenograms. The presence of a necrosed mass is rather important, because in a way, it determines the line of treatment, for when a necrosed mass is present spontaneous resolution is not likely to occur. Out of the 28 cases, 5 had multiple and 23 had solitary abscesses. Bronchographic examination can be done after the acute stage. It is of confirmatory help in the localisation of the lesion especially as regards its segmental distribution. It was done in 5 cases in this series. In others it was not considered necessary. In four cases it demonstrated that the bronchus leading to the opaque area was blocked. The fifth showed cylindrical bronchiectasis indicating the cause of the abscess.

Bronchoscopy was performed in 5 cases because of a suspicion of bronchial neoplasm. It did not furnish any additional or positive help in these as regards their diagnosis or localisation. I must admit that the efficacy of this procedure in diagnosis or treatment depends very much on the bronchoscopist, his efficiency and practice in this art. Bronchoscopy is, in fact, essential to diagnose cases of abscess secondary to a bronchial neoplasm which are not rare entities and so some physicians advocate this in every case. We have in fact, now started following such a procedure.

AETIOLOGICAL FACTORS

No effort must be spared to search for the primary cause of every lung abscess. The elucidation of the cause may have a profound effect on prognosis and treatment, besides enabling us to understand the means of prevention of other cases.

Stern[9] (1935) investigated 115 cases from this point of view and found :—

Post-operative	30%
Other causes	6%
Unknown	64%

Out of this unknown group 84 per cent showed gross dental sepsis. Brock[2] (1947) in an analysis of 363 cases collected from records of cases over a period of about 10 years, gives the following data :—

1.	Bronchial carcinoma	13%
2.	Post-operative	25%
3.	Dental sepsis	19%
4.	Various causes	18%
5.	Specific infections	8%
6.	Obscure primary	30%

This series of 28 cases cannot be considered important or conclusive for ætiological analysis. Our future work will show what the important causes are in the cases we meet here. However in this series of 28 cases the ætiological factors were as follows :—

After dental extraction, *i.e.*, post-operative	1
Heavy dental sepsis present with no other obvious cause	13
Bronchiectasis and cyst in lung (two confirmed by bronchography)	4
Specific infection	2
Pyæmic	1
New growths	4
Unknown causes	2
Foreign body	1

Post-operative :—The incidence of post-operative lung abscess has varied in the analysis worked out by different observers. Certain American workers such as Flick[4] and George[5] ascribe to this group 60-70 per cent of their cases—with tonsillectomy blamed as the worst culprit, while Brock[2] ascribes to this group only 25 per cent of the abscess cases analysed by him.

In our group we find dental extraction, (*i.e.*, post-operative) to be the cause in only one case. This patient developed in 1940, about 15-20 days after a tooth extraction, fever, pain, cough and foul smelling sputum. It is thus probable that she had developed then an attack of acute fœtid abscess. According to her statement she recovered fully from this. However, later on, symptoms like cough, expectoration, hæmoptysis and fever began to recur indicating that she never probably fully recovered but that from the old focus, repeated attacks of fresh pneumonitis were occurring. She ultimately developed multiple abscesses in her right lung.

We come across very few post-operative abscesses here. Our surgeons, in the general as well as the nose and throat side, state that they hardly ever see a post-operative lung abscess.

I want only to say, that as the above case suggests, a more careful follow up, a more extensive use of roentgenology and a close liason between the surgeon and the physician might reveal a greater number of such cases.

BRONCHIAL EMBOLISM

According to Brock[1], the commonest mechanism in the production of lung abscess is bronchial embolism, oro-nasal sepsis, particularly septic gums and teeth encrusted with tartar, constituting the most common source of emboli. 'It was once thought that as quite many—if not the majority—of abscesses occur in the right upper lobe and not the lower lobe, the origin of the abscess lies in vascular embolism and not in aspirations in the majority of cases. A fair incidence of abscesses even after abdominal operation was also considered to prove the same contention. It is therefore surprising that with advances in knowledge these very facts have become rather a strong argument in favour of the idea of bronchial embolism, as opposed to vascular embolism, as the most important cause of these abscesses. Thus, one of the most conclusive facts to prove the bronchial embolic contention is the more frequent occurrence of abscesses in the right as compared to the left lung, and especially in certain sites in the lungs which are particularly favourably placed to receive the inhaled material in certain common postures of the body These sites are the posterior and axillary portions of the sub-apical (postero-lateral) segments of the upper lobes and the apical (superior) segment of the lower lobes. Brock pointed out this fact before the medical Society of London in 1938. He postulated that when the patient is lying on the back, as for example, after an abdominal operation the apical (superior) bronchus of the lower lobes is the first bronchus encountered by the material flowing along the posterior wall, while when the patient is lying wholly or partly on his side, it is the sub-apical (postero-lateral) bronchus of the upper lobes that is the most favourable site.

Brock's analysis of lobar distribution of 50 cases is as follows :—

Right upper lobe ..	20	Left upper lobe ..	6
Right middle lobe ..	3	Left lower lobe ..	9
Right lower lobe ..	12		

The right lung is involved in 35 as compared to the left lung in 15.

A similar analysis of our present series of 28 cases shows the following distribution :—

Right upper lobe ..	6	Left upper lobe	5 (lingular 3)
Right middle lobe ..	3	Left upper lobe	6
Right lower lobe ..	5		

(one of the above cases had 2 abscesses).

All lobes—right lung.. 2

Bilateral (with more than 2 abscesses) 2

Segmental distribution of abscesses :—

Post sub-apical (or postero-lateral) branch of right upper lobe 3

Posterior sub-apical (or postero-lateral) branch of left upper lobe.	1
Axillary sub-apical branch of right upper lobe ..	1
Right middle lobe	3
Lingular segment	3
Apical (or superior) and sub-apical (or sub-superior) segment of right lower lobe	4
Apical (or superior) and sub-apical (or sub-superior) segment of left lower lobe	4
Basal segments of right lower lobe..	1
Posterior basal of left lower lobe	2

The segmental distribution of cases with bilateral abscesses, and where an abscess had involved more than one segment, has not been included. So the total of above cases is only 22.

It will be noticed that the right lung was involved in 16 as compared to the left lung in 11, which is not a very striking difference so far as this series is concerned.

This analysis of 28 cases also demonstrates another interesting point, *i.e.*, in the case of the left lung unlike the right lung, there is a greater involvement of the left lower lobe as compared to the left upper lobe.

This difference becomes still marked if the lingular abscesses are excluded from the left upper lobe involvements.

Left upper lobe	2
Lingular	3
Left lower lobe	6

Even in the case of Brock's series there was greater involvement of the left lower lobe (9) as compared to the left upper lobe (5), but no explanation, so far as I know, seems to have been given by him for this finding.

Bawa, who assists me in the Chest Clinic and who has assisted me in writing this paper, conducted the same experiment as was done by Brock and studied the behaviour of a small amount of radio-opaque oil, acting as a small embolus in 16 cases (besides confirming the same findings in routine cases).

1-2 c.c. of lipoidol was put in the trachea in different postures and radiograms were taken after 1-2 minutes. The above experiment proved that material entering the trachea flows directly to those parts in which abscess and pneumonitis and even tuberculosis most commonly occur. In the case of the right lung the findings were as follows :—

1. Lying supine, the embolus goes to the apical (superior) branch of the right lower lobe. This confirms Brock's findings for this position.

2. Lying supine but the patient partly turned to the right almost at an angle of 45 degrees :—The site of election is the axillary sub-apical

(postero-lateral) branch of the right upper lobe (Figure 2) Brock expects such a result though he does not specifically mention it. In this position, the embolus also sometimes goes to the posterior sub-apical branch of the right upper lobe.

3. When turned completely to the right and lying in a lateral position, at an angle of 90 degrees, the embolus goes to the posterior sub-apical branches of the right upper lobe (Figure 3). This also confirms Brock's findings for this position.

In the case of the left lung, however, the behaviour of the embolus differs rather in an interesting manner from that of the right lung.

4. A patient lying supine and slightly turned to the left at about an angle of 5 degrees the embolus goes to the apical (superior) branch of the left lower lobe (Figure 4.)

5. The difference from the right lung is rather marked when the patient is lying partly or wholly to the left side. Here, in these positions, the embolus is more liable to go to both the lingular and apical (superior) and sub-apical (sub-superior) branches of the left lower lobe rather than the usual branches which are the common sites in the case of right lung, *i.e.*, the sub-apical (postero-lateral) branches of the upper lobes (Figure 5.). So far as I know, Brock is silent on this point.

So far as I have been able to find out, Brock or any other worker has not tried to explain why the left upper lobe abscesses especially if we exclude the lingula, are so uncommon as compared to the left lower lobe abscesses and why the position in this respect is quite the reverse of what we see on the right side. The above experiment, however, gives an obvious explanation of the findings. This experiment would also lead one to conclude that the left lower lobe abscesses should be quite common as the left lower lobe gets the embolus with a person very slightly or completely turned to the left. Our small series so far supports this idea. We hope to deal with this point in detail in a separate article at a later date.

Nicolson[7], in his Goulstorian Lectures for 1950 on the subject of Suppurative Pneumonitis, also accepts this bronchial embolism theory as a cause of these abscesses. In his opinion, when bronchial embolism by small particles occurs, the resulting atelectatic area may in some cases go on to a benign pneumonitis and in others to a suppurative pneumonitis. Of course, cases treated very early are likely to show a resolution before suppuration actually occurs unless the obstruction to the bronchus is gross.

Dental Sepsis.—Oro-nasal passages, specially gross dental sepsis associated with tartar deposits and gum retractions is considered the most common source of bronchial embolism leading to lung abscess. Naso-pharyngeal sepsis can of course behave in a similar manner. In Stern's[9] analysis of 115 cases, 64 per cent were due to unknown causes,

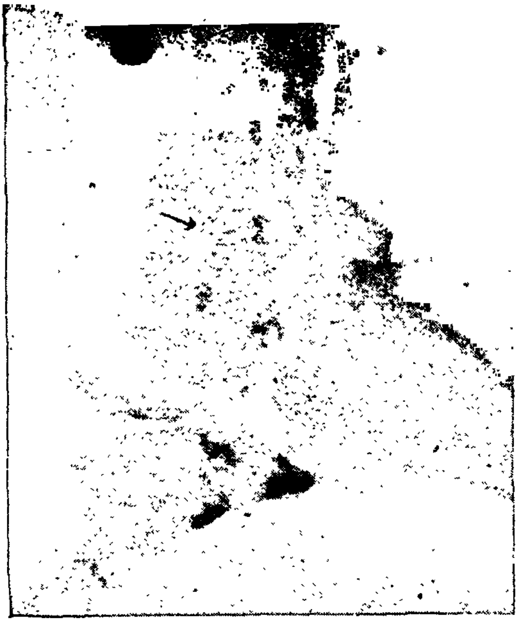


Fig. 1.—1-2 cc. of lipiodol injected, patient lying supine. Lipiodol going to apical (superior) branch of R. L. L.—Lateral View.

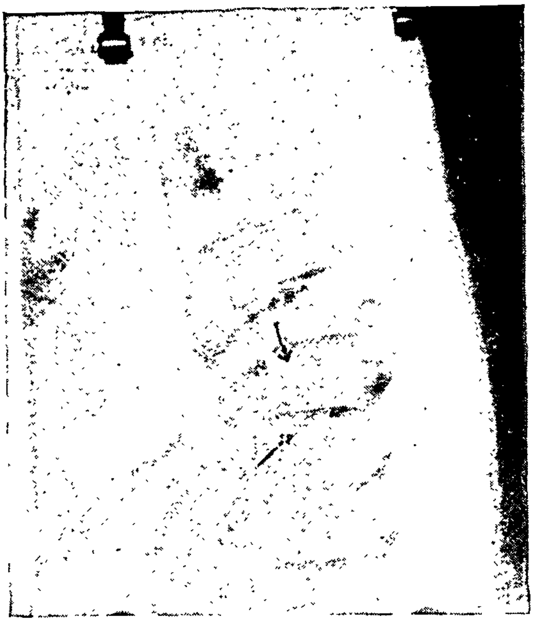


Fig. 2.—1-2 c.c of lipiodol injected—patient lying supine, turned to right at an angle of 45 degrees. Lipiodol going to axillary sub-apical (postero-lateral) branch of R. U. L.—Lateral View.

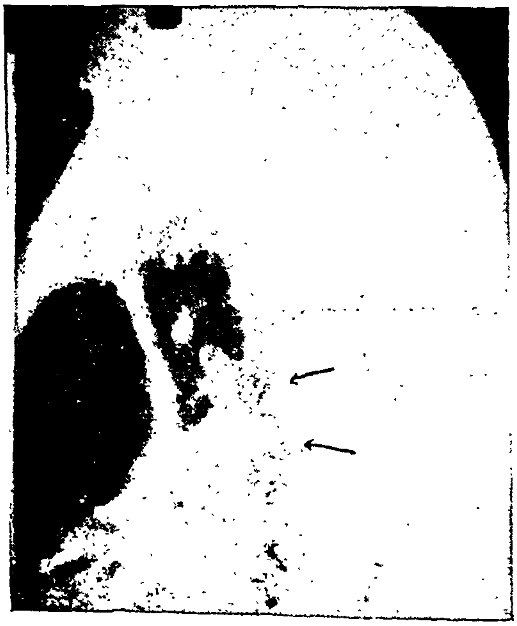


Fig. 3.—1-2 c.c. of lipiodol injected—patient lying in right lateral position, *i.e.*, turned to right at an angle of 90 degrees. Lipiodol goes to posterior sub-apical branch of R.U.L.—Lateral View.

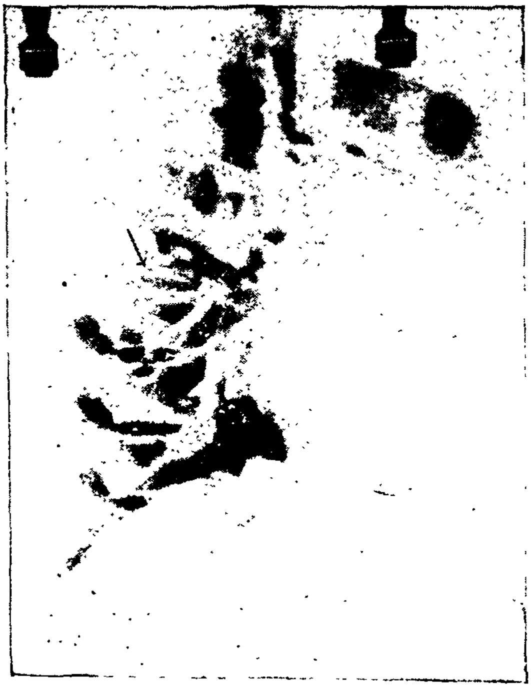


Fig. 4.—1-2 c.c. of lipiodol injected, patient lying supine slightly turned to left—5 degrees. Lipiodol going to apical (superior) and sub-apical branches of L. L. L.—Lateral View.

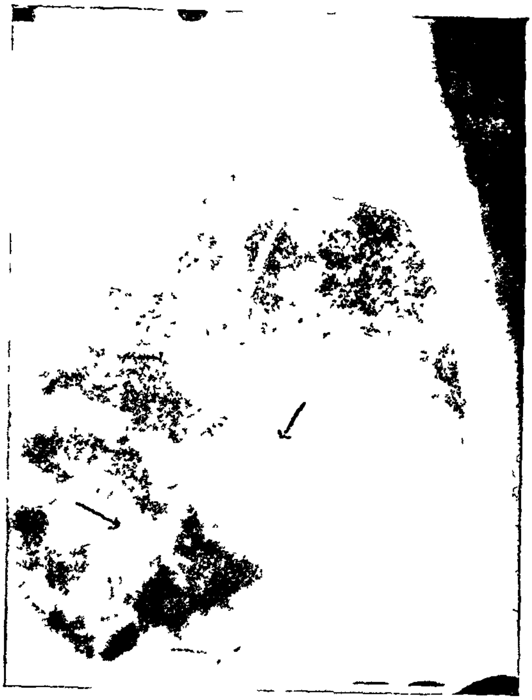


Fig. 5 —1-2 c c of lipiodol injected, patient lying in left lateral position, *i e*, turned to left at an angle of 90 degrees Lipiodol goes to apical (superior) branch of L L L. and lingular branches besides sub-apical branches of L U L —Lateral View.

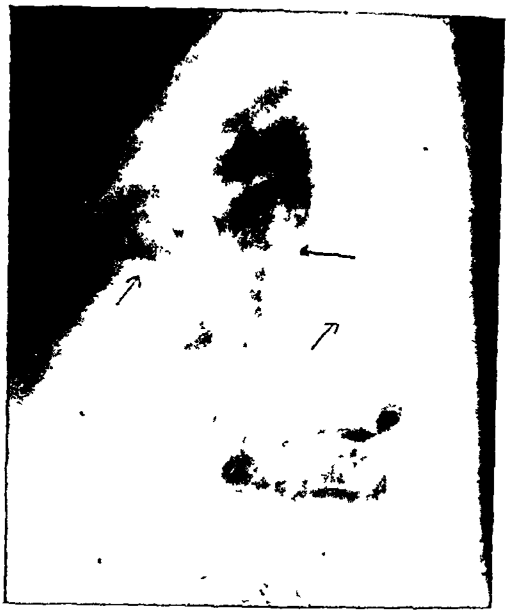


Fig 6 —Post operative lung abscesses--Lateral View Two abscess cavities are seen in R. U. L one in the pectoral and the other in the axillary area. Third abscess cavity is seen in the apical segment of R. L. L

Fig. 7.—A. P. view of the same case after pneumonectomy.

Fig. 8.—A. P. view of a case of cystic lung Right lung shows a bizarre network There was no displacement. Note that the lung markings are very much less in the peripheral part of right lung. This was a common feature of most of the cystic bronchiectasis cases

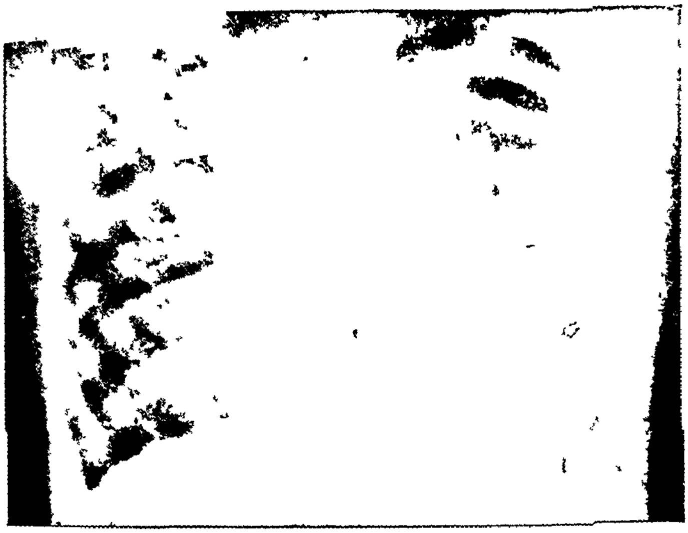


Fig 9.—A P view of the same case after bronchography. The cavities filled with lipiodol are regular and the bronchi are not distorted

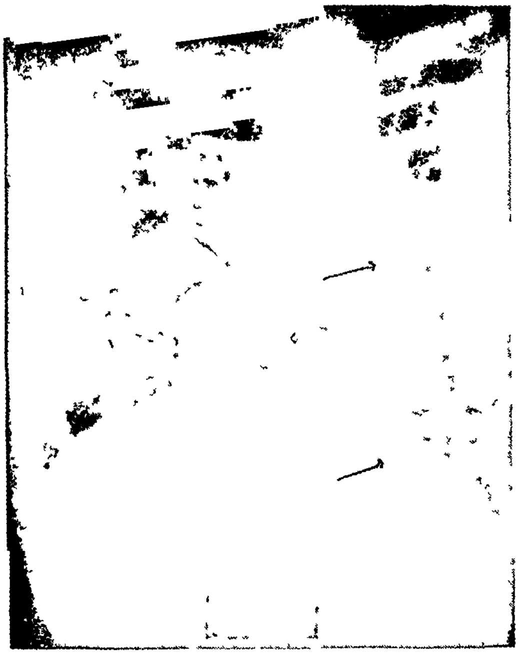


Fig. 10.—A P skiagram of a case shown both cystic and bronchiectatic changes in t same lung Note that in the left lung t dilatations are cystic in character in t upper part, while in the lower part typical sa culated and cylindrical bronchiectasis is see

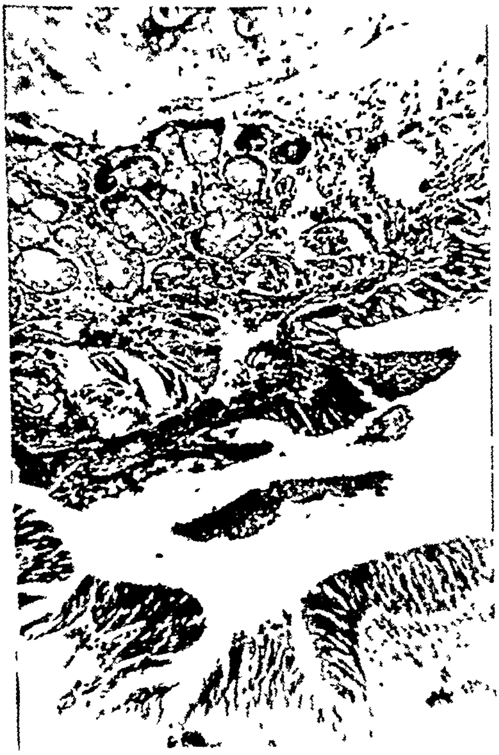


Fig. 11.—Section of resected lung tissue from a case of cystic bronchiectasis. Histologically the tissue shows dilated bronchi lined by ciliated columnar and at places cuboidal epithelium. The walls show smooth muscles, cartilage and mucus glands. The large cysts are similar except that the smooth muscle, mucus gland and cartilage are less abundant and irregular in distribution. Collections of round cells are also seen.

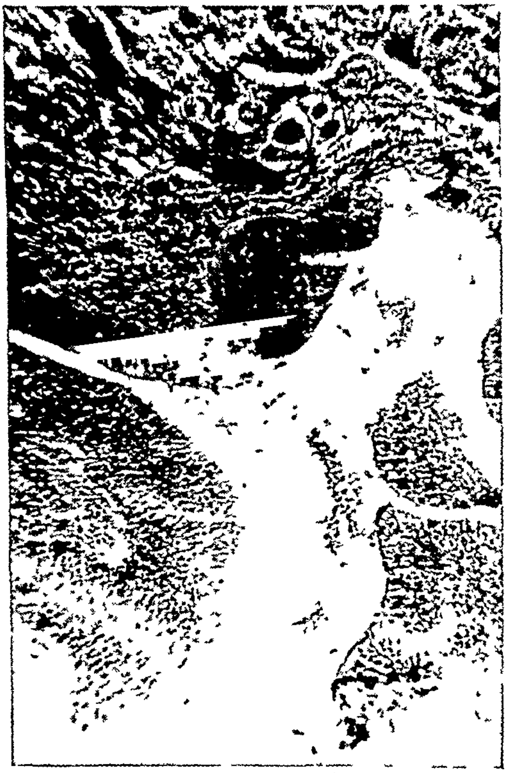


Fig 12.—Section of resected lung tissue from a case of bronchiectasis Section shows dilated bronchi lined with columnar epithelium. The walls are infiltrated with round cells and vessels show dilatations and congestion. At places the cartilage is also seen. Cartilage and mucus glands are seen but diffusedly infiltrated with round cells. There is marked hypertrophy and hyperplasia of the epithelium lining the bronchi.

and as already stated, 84 per cent of this unknown group had teeth coated with tartar and had marked dental sepsis as compared to 12 per cent in the control group.

Brock[1] attaches great importance to the recognition of this as an important cause of lung abscess especially of that which is termed as 'Idiopathic Lung Abscess.' In his analysis of 363 cases, 19 per cent are said to be due to dental sepsis. In this series of 28 cases, marked dental sepsis along with teeth encrusted with tartar, was present in 22 cases. It has been considered by us to be the most probable cause in 13 of our cases. In a control group of 50 taken at random in the Out Patient Department, dental sepsis was found in 7 cases only.

Bronchial Neoplasm :—We have included only those cases of neoplasm in this series who came in as lung abscess cases but were diagnosed later to be lung suppuration secondary to neoplasm. Most workers give the percentage of lung abscess caused by such growths to be about 10 per cent. In this group, it is difficult for us to form an absolutely accurate idea as regards the importance of this factor in the ætiology of lung abscess, as biopsy examination was not possible in any of the cases, while sputum and bronchoscopic examinations did not prove conclusive or even helpful. All the same, depending upon roentgen and clinical evidence, I think that at least 4 cases of lung abscess in this series were secondary to such neoplasms. A roentgenogram of one of them is being shown. In another, the presence of an enlarged hard gland in one axilla and a slow on coming hemiplegia with aphasia due to secondaries in the cortex left no doubt about the ætiology.

Pyæmic Abscess :—One case had multiple abscesses in both lungs, three in all. These were not in regions in which abscesses are commonly found—one being in the right post basal and the second in the left post basal and the third in the right axillary area. The patient was very toxic and had marked abdominal pain in addition to chest symptoms at the onset of his illness. While we were trying to find the ætiology of his abscesses, he suddenly developed a scrotal abscess. He had markedly septic teeth, and a careful examination showed that he had a small anal fistula. His sputum showed a positive culture for *B. Coli* indicating the cause to be anal fistula. This finding greatly helped us in making the proper choice for chemotherapy which cured him completely.

Specific causes :—Bacteriological investigations did not prove of much help to us either in the diagnosis or in formulating the line of treatment. The reason is obvious. Cases came to us late, *i.e.*, many weeks after the onset and always many days after the abscess had ruptured into a bronchus. So by the time they came the flora was already mixed. It is on clinical grounds and not on the basis of bacteriological proof that we have stated that two abscess cases were due to specific infections.

One of the cases was in fact definitely specific. In this the abscess in the lung had started secondarily to an amœbic liver abscess which had burst into the lung. The other was a mali, very poorly clad, who sat all the night in the open field watching his master's buffaloes. He started with high fever and pain in the chest the next morning. He joined the hospital a few days later with multiple abscesses in unusual situations. It is possible that these were due to some specific infection going on to bronchopneumonia after exposure to cold, which in turn went on to suppuration. Culture of the sputum showed a mixed flora.

As discussed above and shown in our figures, 13 of the abscesses have been ascribed definitely to certain causes such as bronchial embolism after operation or due to bronchiectasis, foreign body, pyæmia and specific infection. This however still leaves 15 cases.

As regards this group, I may state that 13 of them had marked dental sepsis, and all had abscesses in sites favoured by bronchial emboli, unlike the pyæmic, neoplastic and specific cases. It is reasonable to assume that they were actually the result of bronchial emboli.

Treatment :—A lung abscess not being always due to the same ætiology, the primary cause and nature of suppuration must, if possible, be first determined, before a proper line of treatment can be chalked out. Neoplasms especially must be ruled out.

Natural resolution by medical treatment, consisting of rest, chemotherapy by the intramuscular route or by ærosols, postural drainage and high protein diet, would be an ideal termination of lung abscess. However, when the patients come to us in a stage in which they usually present themselves first, *i.e.*, after a lapse of about 2 months from the onset, medical treatment is not of much avail. The analysis of medical treatment of 28 cases of this series is as follows :—

Cured	5	(They were all acute abscesses).
Passed on to chronic stage	19	
Deaths	4	(while in hospital).

Many more must have died after discharge from the hospital. If we take only the acute cases, *i.e.*, those who reported within 6 weeks, 5 out of 9 such cases got cured showing that medical treatment can be effective in a fair percentage of such cases. However, radiologically, some degree of fibrosis is always left and it is not cetain if a small focus of suppuration is not still left in them which may flare up again at a later date, as a mild amount of expectoration also often persists in them.

Surgical Treatment :—External drainage with rib resection was done in 3 cases. One of these showed clinical improvement though the cough persisted. Later, by bronchography, it was found that he had cylindrical bronchiectasis of the basal branches. The other case had multiple abscesses and so showed no improvement. Later, a successful pneumonectomy was done on her at Vellore by Dr. Betts. The third had a lung abscess secondary to a dermoid cyst and is still under treatment.

According to Smith[8] (1948), with treatment under medical lines 19 per cent of cases got cured and 60 per cent became chronic as compared to 46.1 per cent cured and 21.2 per cent chronic with surgical treatment.

Recent statistics by certain workers on the treatment of acute abscesses by chemotherapy, since the advent of penicillin by the intramuscular route or ærosols, are more hopeful. Jewett[6] and Dimond claim 10 cures in 12 cases treated by combined parenteral and ærosolized penicillin therapy. They however admit that only acute cases in which the duration of symptoms has been less than 12 months are good subjects for medical management. It must also be remembered that the results of surgical treatment are also improving as more cases are being rendered fit for resections by the use of chemotherapy.

On the whole I think that medical treatment is more or less a failure so far as the cure of chronic cases are concerned, though with proper medical measures the patient does improve to a point where he becomes a better surgical risk.

BRONCHIECTASIS

Aetiology :—It is now almost universally accepted that obstruction to the lumen of a bronchus produces atelectasis, and bronchiectasis develops on the top of that. Obstruction of a bronchus is probably most commonly caused by viscid secretions. This is especially so in childhood. Other factors are foreign bodies, bronchial neoplasm, bronchial stenosis and fibrosis from various causes.

In this series of 22 cases of bronchiectasis, 15 males and 7 females, nearly all confirmed by bronchography, a foreign body was the cause in 2 cases.

In three cases of this series it was found to be secondary to tuberculosis.

Examination of the teeth showed thickly coated teeth and septic gums in 9 cases out of 22 patients. Six cases had congested throats. One case had a septal defect with discharge from both meatuses, while two cases had hazy sinuses.

It is possible that a more careful examination of the oro-nasal passages may show a closer association between the two.

Bronchography should always be done in every suspected case of bronchiectasis.

Of course, if an operation is to follow, all the lobes of both lungs should be subjected to bronchography.

Bronchography was done in 31 suspected cases out of which 19 showed positive and 12 negative results. The 'Leafless Tree' appearance was universally present.

Plain roentgenograms cannot be regarded as decisive for final diagnosis.

CYSTIC LUNG (MAINLY CYSTIC BRONCHIECTASIS)

Due to certain characteristic radiological findings these could be grouped together.

Out of our group, 19 of our cases fall into the group of cystic bronchiectasis. One had a solitary, suppurating cyst which turned out to be a dermoid cyst. She is not being included in further analysis.

The characteristic features of our main group are that the cystic cavities are regular and freely communicate with the bronchi. Bronchi in some cases show fusiform dilatations in addition to the cystic dilatations. Such fusiform dilatations are however not distorted as in the usual cases of bronchiectasis. A bizarre network is often visible in the plain roentgenogram along with lessened lung markings in the periphery of the lung field. Generally, there is no marked displacement present unless there is a massive involvement of the whole lung. However, this is seen definitely in some cases.

TABLE 1.—*Incidence According to Age Groups.*

Ages at which patients reported (in years)	0–5	6–10,	11–15,	16–25,	26–40,	41–50,	51–70
Cystic lung	1	2	4	6	3	3	..
Bronchiectasis	..	..	..	5	9	2	6

TABLE 2.—*Appearance of Symptoms According to Age Groups.*

Ages at which symptoms appeared (in years)	0–5	6–10,	11–15,	16–25,	26–40,	41–50,	51–60
Cystic lung	7	2	2	6	2	..	..
Bronchiectasis	1	..	3	5	6	4	3

TABLE 3.—*Degree of Lung Displacement.*

Displacement	No. displacement	Slight dis.	Moderate dis.	Marked dis.
Cystic lung	11 (58%)	3 (16%)	4 (21%)	1 (5%)
Bronchiectasis	14 (63%)	3 (14%)	2 (9%)	3 (14%)

TABLE 4.—*Involvement of Lobes.*

Lobes involved	R.U.L.	R.M.L.	R.L.L.	L.U.L.	L.L.L.
Cystic lung	6	4	6	3	9
Bronchiectasis	6	6	9	2	7

Tables 1, 2, 3 and 4, show a comparison between the ordinary bronchiectasis and cystic bronchiectasis as regards the displacement, lobar distribution and age of onset, etc.,

In all these cystic cases there was a history of cough and expectoration of varying duration. 8 gave history of acute illness resembling pneumonia. It is, however, difficult to say if it had any casual relation with the cystic condition or was in fact a complication of a cystic state. They ultimately end either in some serious complications such as suppurative pneumonia or in Cor Pulmonale.

A very interesting question is whether these cysts are a congenital anomaly or are an acquired state and what their relationship is with bronchiectasis.

The very fact that almost in one year we have been able to detect as many as 19 cases, goes strongly against the condition being congenital. I think the condition is quite common provided one is on the look out for it. Another clinical feature which goes strongly against the congenital hypothesis is the fact that quite a number of them started quite late in life. Lack of displacement of the mediastinum, etc., in the majority of such cases is often mentioned as a point in favour of these being congenital, as bronchietasis being the result of atelectasis is supposed to be far more often accompanied by mediastinal displacement. Table 3, however, shows that the percentage of cases showing no displacement in the two conditions is practically the same, though marked displacement is more frequent in bronchiectasis. I may also mention that none of these cases were associated with any other congenital disorder though I am quite aware of the reports of a few cases by different observers, where cysts in the lung were found associated with conditions like tuberose sclerosis, xanthomatosis, biliary cirrhosis, pituitary disorders, etc. However one point is striking and may be considered at first sight to strongly support the theory of the congenital origin of these cysts. The onset of the symptoms is on the average at a much younger age in this group than in the usual bronchiectasis group. However this need not necessarily mean that the condition of cystic disease is congenital in origin. It is in fact possible that it is the state of the bronchial walls that determines whether, when atelectasis has occurred, the dilatations will become cystic in shape or will remain fusiform or saccular. The cystic dilatations may thus depend upon a special congenital weakness of the bronchial wall, or because in childhood, or infancy the bronchial walls are yet so poorly developed that they give way more easily to a pull. Considering that a certain number of cases develop much later in life, much may also depend upon the site of obstruction causing atelectasis and whether that is viscid sputum or some other physical agent. It is well known that when bronchiectasis affects the larger bronchi the result is cylindrical bronchiectasis and when it affects the smaller bronchi the result is saccular dilatations. It is possible that when still smaller bronchi are affected the result is cystic dilatation. According to such a hypothesis cystic lung of this type is just a variety of bronchiectasis, the varieties being fusiform, saccular, and cystic. Moreover, it is possible that due to the ineffective nature of the cough in childhood and infants, the bronchial emboli of viscid sputum more often reach the smallest branches of the bronchi.

Another suggestion which I am hazarding may be worthy of consideration. While the ordinary type of bronchiectasis may be the result of atelectasis, as is commonly believed, the cystic type may form in the same way in which tension cavities or localised patches of emphysema form, *i.e.*, when the obstruction remains partial so that air can enter during inspiration but cannot leave during expiration. This may possibly result in the cyst-like ballooning of the bronchi beyond the obstruction especially if their walls are already weakened by inflammation.

Two other theories as regards the formation of such cysts deserve some mention. It has been postulated that as the majority form in childhood, they may be the result of the primary type of tuberculosis, formed by a gland pressing upon a bronchus or eroding into it, and causing atelectasis. While it is possible that a few cases may develop like this, the preponderance in the lower lobes goes strongly against such a hypothesis. If it be tubercular glands causing it, the distribution should be anywhere in the lungs and, if anything, the middle lobe cysts should preponderate as the bronchus of this lobe is most susceptible to such pressure.

Nicolson[7] and others have suggested that these cysts may be the result of epithelization of old healed abscesses. While such a theory may explain some of the solitary cysts, it is difficult to visualize small multiple abscesses even in a single segment leaving the multiple cyst-like cavities that we find. Moreover, lack of any marked distortion of the bronchi in many of the cases goes strongly against such an hypothesis.

Three of our cases throw an interesting light on the subject and rather go to show that the two conditions are identical. One of the cases developed bronchiectasis after inhalation of a foreign body with secondary suppurative pneumonitis. A careful examination of his bronchogram shows that while he had developed the usual type of bronchiectasis, a few of the shadows showed an appearance very similar to that of cystic dilatations. The other two cases are even more suggestive. They had the usual history of bronchiectasis and were aged about 30 years. The bronchograms showed that while certain areas show saccular dilatations, in other areas the appearances are typical of cystic disease. It would thus, I think, be rational to assume that the two conditions are just different grades or types of the same disease unless the pathologists can definitely prove that the two conditions are different which they have not been able to do so far.

Due to lack of time I would say that only a few cases have so far been submitted to major surgery like pneumonectomy and lobectomy in this hospital but we are developing such units.

I may say that, however, the only hope for chronic cases suffering from the clinical entities discussed in this lecture, lies in surgery. I think we should all try in our own way to have a Chest Surgery Unit in every premier hospital in a state. The need of such units is great, specially when we consider the fact that lobectomies and pneumonectomies are going to play an important role even in the treatment of pulmonary tuberculosis, in addition to being the sole curative procedures for the majority of cases of bronchiectasis and chronic lung abscesses. In addition chest surgery is likely to play an important and ever increasing role in the treatment of many heart conditions. Of course, an alternative method for a country like ours where every state is passing through financial stringency, can be that we may develop to start with a few chest surgery centres in India, where chest surgeons and other auxilliary services can be made available to patients from different parts of the country and where surgeons from different states could be sent for training in this art so that in the course of time every state could have a well established Chest Centre of its own.

REFERENCES

1. Brock, R. C.: Observations on Anatomy of the Bronchial Tree with Special Reference to Lung Abscess, Guy's Hosp. Rep. **91** : 111-130, 1942.
2. Brock, R. C.: Studies in Lung Abscess, Aetiology of Lung Abscess, Guy's Hosp. Rep. **96** : 141-168, 1947.
3. Brock (1948) : The Anatomy of Bronchial Tree (see 2).
4. Flick, J. B., *et al*: Pulmonary Abscess, Analysis of 172 Cases, Arch. Surg. **19**: 1292-1312, 1929.
5. Georg, C. Jr.: Medical Treatment of Abscess of Lung, Thorac. Surg. **1** : 650-654, 1932.
6. Jewett and Dimond, Dis. of Chest. 1950.
7. Nicholson, H.: Suppurative Pneumonia, The Lancet, **2**: 549-554, &605-611, 1950.
8. Smith, D. T.: Medical Treatment of Acute and Chronic Pulmonary Abscess. J. Thorac. Surg. **17** : 72-90, 1948.
9. Stern, L.: Putrial Abscess of Lung Following Dental Operations, J. Thorac. Surg. **4** : 547-557, 1935.

ORIGINAL ARTICLE

A PRELIMINARY REPORT ON EXPERIMENTAL EPIDEMIC DROPSY

B. B. Bhatia and B. K. Malaviya *

Careful study of the clinical picture of epidemic dropsy, from the literature, and our own observations of cases occurring in the Uttar Pradesh State, convinced us, that the clinical picture was not uniform in different epidemics and showed considerable variation. Was this variation due to different adulterants in the mustard oil or some other factors ? What was the pathogenesis of epidemic dropsy? Was vitamin B complex, which was so largely administered, of any use in the treatment of this disease? These were some of the questions that baffled us and made us undertake an experimental study of epidemic dropsy. The work has been in progress for over a year and a half but we are still in the preliminary stages. We have ventured to present a brief report of the work done so far at this meeting of the eminent physicians of India, so that their criticism and suggestions may be of help in our further work.

By the kind permission of the Govt. of the Uttar Pradesh State—we were able to produce an epidemic dropsy-like syndrome in volunteers from the Lucknow, Central Jail. The Govt. agreed to give some concession to these volunteers and we agreed to compensate them and their families, if any permanent harm came to them. One of the volunteers was used as control and was given one ounce of pure mustard oil daily with his usual well balanced diet, the other five were fed on mustard oil adulterated with 10 per cent *Argemone mexicana* oil.

In each case a thorough clinical examination, including teleradiogram, electro-cardiogram, visual fields, tension of the eye balls, etc., was done before the experiment was started; symptoms were noted from day to day and a thorough clinical examination was made at weekly intervals.

Daily feeding of the oil was continued for 28 days; after that, we could not persuade the volunteers to continue it, as their suffering was rather acute. However during this period we had succeeded in producing an epidemic dropsy like syndrome in all the five volunteers, who were given mustard oil, adulterated with that of *Argemone mexicana.*

The symptoms produced in the control and the five volunteers are given below in Table 1. The control was not told that he was being given a different oil and for the first 2 or 3 days exhibited the same symptoms as the others, but did not develop any anasarca. From the

---

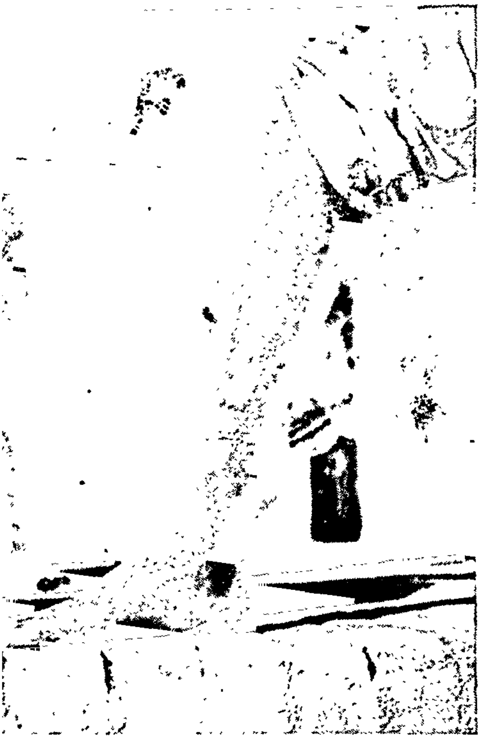
* Department of Medicine & Biochemistry, Lucknow University.

TABLE I.—*Symptoms Produced in Human Volunteers After Administration of Mustard Oil Adulterated with 10% Argemone Mexicana.*

Name	Age and Sex	Gastro intestinal.	Cardiovascular.	Nervous.	General Anasarca.	Eyes.	Skin.	General.
R. B. (Control).	32 M	Burning sensation stomach, vomiting and loss of appetite for a couple of days.	No symptoms ..	Tingling sensation in legs which disappeared after 2 days.	Nil. ..	No symptoms ..	Pigmentation on the feet.	Weight dropped from 146 to 143. No other symptoms.
D.	39 M	Pain in the abdomen. Griping. Bouts of diarrhoea. Occasional vomiting, throughout the period of experiment.	Exertional dyspnoea after ten days.	Burning and tingling all over the body.	after 7 days Nil. after 14 days + after 21 days ++		..	Pain all over the body. Malaise. General weakness.
L. H. ..	35 M	Vomiting. Diarrhoea. Loss of appetite. Twice severe abdominal pain.	Exertional dyspnoea after 12 days.	Burning and cramping sensation.	after 10 + days .. after 14 days .. ++	No symptoms. ..	..	Burning and cramping pain all over the body. Slight temp. Malaise. Extreme weakness.
H.	36 M	Diarrhoea, Griping. Pain. Loss of appetite.	Exertional dyspnoea after 14 days.	Tingling and sensation of creeping ants.	after 7 days Nil. after 14 days + after 24 days ++		..	General weakness. Malaise. Great distress Refusing all food.
M.	34 M	Vomiting. Loss of appetite. Constipation. Sensation of tenesmus. Severe pain in abdomen. Diarrhoea.	Dyspnoea ..	Stiffness of the thigh. Tingling sensation hands and feet.	after 7 days+ .. after 14 days ++ after 21 days +++	Heaviness of eyes. Dizziness of vision at night.	..	Pain all over the body. Lethargy. temp. 101. Weakness. Agony and distress.
S. R. ..	43 M	Pain and griping. Loss of Appetite and vomiting.	Exertional dyspnoea after 10 days.	Nil. ..	after 7 days Nil. after 14 days + after 21 days ++		Patches of Erythema on legs. Pigmentation of hands and feet.	Headache and pain all over. Lethargy. Pain in joints. Marked weakness and distress.

TABLE 2.—*Signs Produced in Human Volunteers After Administration of Mustard Oil Adulterated with 10% Argemone Mexicana.*

Name	Age/Sex	Cardiovascular System.	Skin.	Eyes.	General Anasarca.
R. B. (control).	32/M	Pulse-Rate—No change Rythm-Sinus arrythmia B, P.-No change Tele-radiogram-no change. E.C.G.-no change.	Slight pigmentation of feet.	Visual fields-no change. Tension Eye ball no change.	Nil.
D.	39/M	Pulse-slowed to 56, Rythm-No change B. P.-No change Tele-radiogram-No change E.C.G.-Q. T. 0.36 to 0.44 Q.T.C. 0.44 to 0.47	No signs	Visual fields no change. Tension Eye ball no change.	Oedema legs ++ After 14 days.
L. H.	35/M	Pulse-slowed to 60 Rythm-Sinus arrythmia. B. P.—Slight fall. Tele-radiogram—No change. E.C.G.—Q. T. 0.24 to 0.42, Q.T.C.—0.28 to 0.42.	No. signs.. ..	Do. ..	Oedema legs. ++
H.	36/M	Pulse-slowed to 60. Rythm-No change. B. P.—No change Tele-radiogram—No change. E.C.G.-Q.T.— Q.T.C.—No change.	No signs	Do. ..	Oedema legs ++
M.	34/M	Pulse-No change. Rythm-No change. B. P.-No change. Tele-radiogram—No change. E.C.G.-Q. T. 0.24 to 0.36 Q.T.C. 0.28 to 0.42.	No signs... ..	Do. ..	Do. +++
S. R.	43/M	Pulse-No change. Rythm-No change. B.P.—No change. Tele-radiogram-No change. E.C.G.-Q. T. No change. Q.T.C. No change.	Patches of erythema and pigmentation feet and legs.	Do. ..	Do. ++



1.—Leg showing œdema +, 10 days after discontinuance of Argemone oil. (Mr. D.)

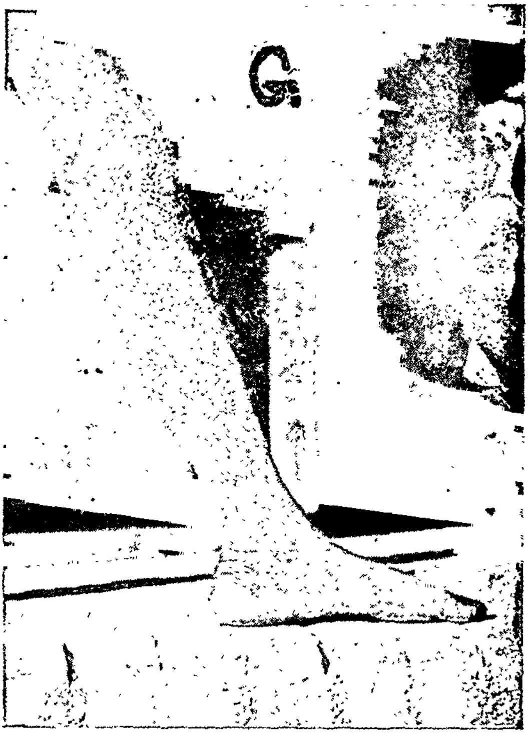


Fig. 2.—Leg showing œdema +, after 12 days of the administration of oil. (Mr. H.)

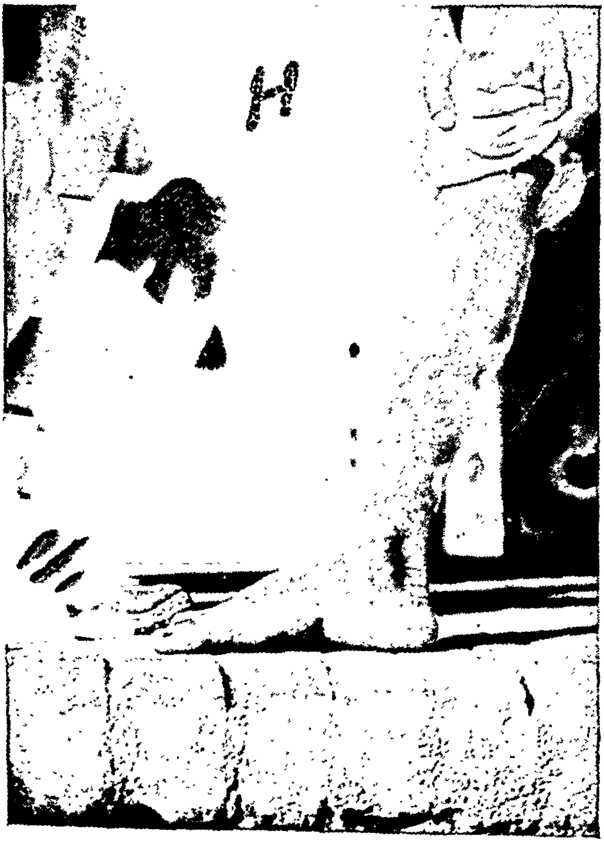


Fig. 3.—Leg showing patches of erythema and œdema, after 14 days of the administration of oil. (Mr. S. R.)

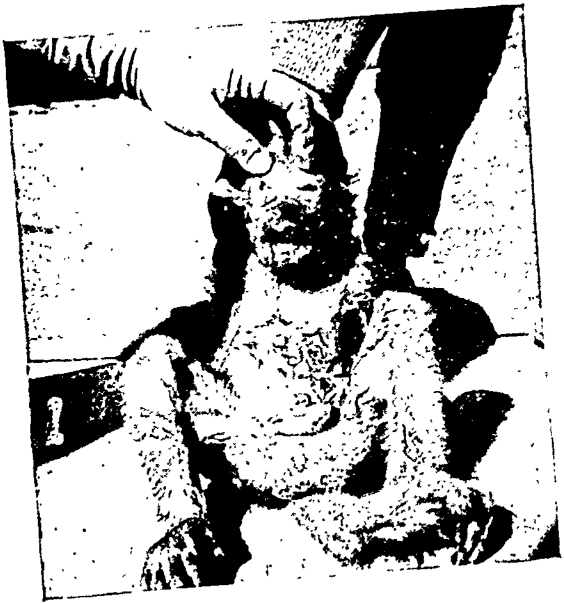


Fig. 4.—Monkey—after 6 weeks of administration of oil—showing erythema general anasarca.

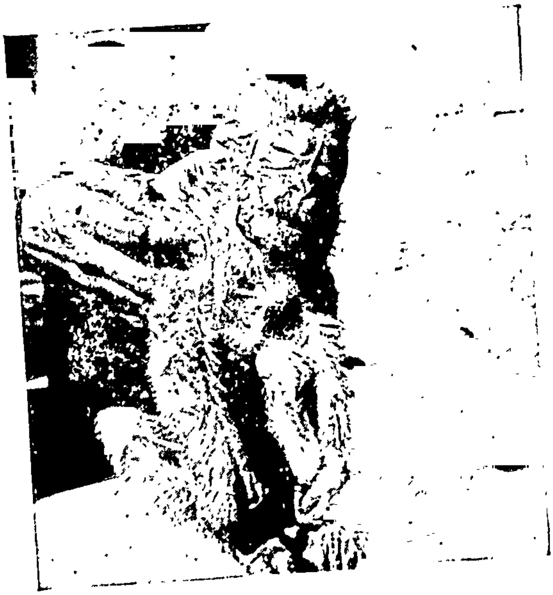
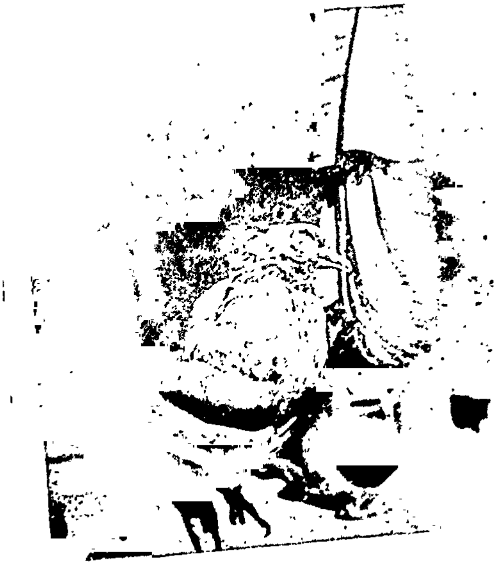


Fig. 5.—Monkey—after 2 months of administration of oil—showing severe œdema, extreme prostration and lethargy.



11

Fig. 6.—Pigeon—on another toxic oil—showing loss of one eye.

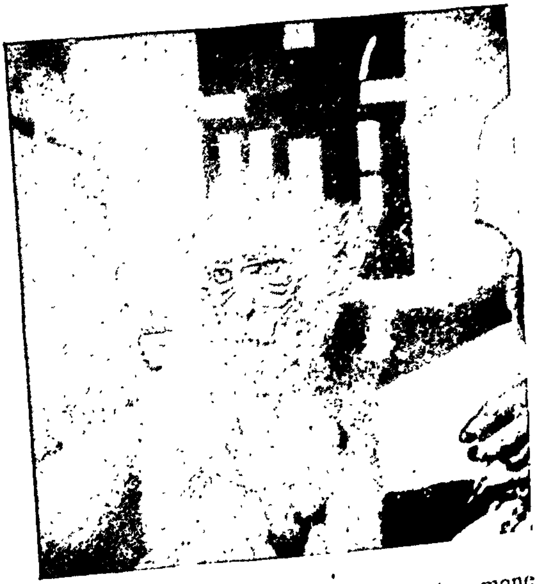


Fig. 7—Monkey—after 10 days of Argemone oil—showing erythema and slight œdema.

perusal of this chart it would be obvious, that severe gastro-intestinal irritation is produced by this oil leading to nausea, vomiting, diarrhœa, pain, griping and loss of appetite. Generalised body pain, malaise and lethargy were also prominent symptoms. All the volunteers, started showing œdema on the feet, after 7 to 10 days of the ingestion of the oil. It continued to increase progressively with the administration and remained for nearly one month, after the oil was discontinued. Photographs 1, 2, and 3 show the type of œdema, which was produced.

In Table 2 are summarised the signs that were noticed on weekly examinations. It would be obvious from its perusal, that no characteristic changes were observed in the cardiovascular system, visual fields or the tension of the eye balls.

As a result of this experiment, we were convinced that the epidemic dropsy-like syndrome could be produced in nearly all cases by the administration of mustard oil, adulterated with 10 per cent *Argemone mexicana* oil, but the clinical picture was somewhat different from that seen in epidemics. For instance, during a period of 2 months of this experiment, one month of oil administration and one month subsequent to that, no cardiovascular signs were noticed, nor were any significant changes found in the heart on clinical, radiological and electro-cardiographic examination. In epidemics, cardio-vascular symptoms and signs have been reported in nearly 85 per cent of cases. In this short series, we also failed to notice any visual symptoms, such as changes in visual fields or in the tension of the eye-balls. Such changes again are said to occur in 10 to 15 per cent of cases of epidemic dropsy. We also failed to observe except in one case any skin lesions, such as erythema, pigmentation, warts or sarcoid-like nodules. The gastro-intestinal and general toxæmic symptoms were far more pronounced in our experimental series than in the naturally occurring disease.

It thus became obvious that in the naturally occurring disease, some other contributory factors were present; these might have been (1) ill balanced diet of different localities (2) other toxic substances in the adulterated mustard oil (3) super-added exogenous infections. Observations on these aspects have been started in a series of animals.

We have also succeeded in producing in rhesus monkeys an epidemic dropsy-like syndrome, exactly similar to that produced in human volunteers. Four monkeys were fed daily with 0.5 cc. of pure Argemone oil by dropping it on the back of their throat by means of a glass pipette. We had to resort to this method, as monkeys refused to eat a meal cooked with this oil. Four controls were fed on daily doses of 0.5 c.c. of pure mustard oil. Those fed on *Argemone mexicana* oil started showing puffiness of the face and œdema of the hands and feet in 10 to 15 days. All of them died after 2 to 3 months by the daily administration of this oil. A careful pathological study is being made of the viscera obtained at postmortem, but unfortunately inspite of all our efforts, the report could not be ready for this conference. Photographs 3 and 4 show the type of disease that was produced in these monkeys. Monkeys fed on pure mustard oil did not show any signs or symptoms. Rabbits and rats were also given *Argemone mexicana* oil—but did not develop any signs.

We have now undertaken a systematic study of the pathological changes produced by the oil—at the commencement of general anasarca—when general anasarca has lasted for one month—two months—and three months—in order to find out the progress of the pathological processes and to determine at what stage it is reversible by the discontinuations of the oil.

We have started a careful study of the hæmodynamics of the cardio-vascular system and the bio-chemical changes. These experiments are likely to last for a long period, but we hope, they will enable us to throw more light on the pathogenesis of this disease.

We have also diverted our attention to find if besides *Argemone mexicana* there are some other toxic adulterants in mustard oil. Various samples of mustard seeds were collected from Lucknow, Bareilly and Banars markets. These showed adulteration with several other seeds besides *Argemone mexicana*. In some cases, the exact identity of seeds was not possible. We have grown these seeds last November and when the plants are mature,their botanical names will be determined.

Meanwhile we have started experiments with one other oil which also seems to produce toxic symptoms but somewhat different from those of *Argemone mexicana*. This oil produced gastro-intestinal symptoms, such as diarrhœa in monkeys, but no general anasarca or erythema. In the pigeon it has produced some ocular changes in all cases. Photograph 6 is a picture of one of these pigeons. However, it is too early to talk about this oil.

ORIGINAL ARTICLE

AUREOMYCIN IN ENTERIC FEVER

Preliminary Communication

B. B. Yodh and B. J. Vakil

Since the introduction of aureomycin by Duggar, two years back, many reports have been published regarding its effects in various diseases. Bryer, Long and others[3] (1948) treated two patients of enteric fever with aureomycin 10 to 16 mg. per Kg. body weight per day and reported favourable initial results. In the same year, Finland, Collins and Paine[4] in their work on sensitivity of various organisms to aureomycin *in vitro* and *in vivo* showed that most of the gram negative bacilli including typhoid and salmonella were inhibited in *vitro* by 25 Gm. per c.c. of aureomycin. They reported five cases of enteric, treated with aureomycin. The results show that blood, urine and stools became sterile in 24 to 72 hours after treatment in all the cases, but effective symptomatic improvement was observed in one case only, two cases showed doubtful improvement, while two cases completely failed to improve. One of the cases developed hæmorrhage and perforation. They also reported temporary sterilization of a typhoid carrier during treatment. Vernon *et al* (1949) reported its effect on two cases treated with a dose of 50 to 500 mg. per Kg. body weight per day. They found that aureomycin had slight but definite effect on their cases, though they mentioned that chloramphenicol was superior. Brainerd, Clark and others[2] (1949) reported effect on three cases of healthy typhoid carriers and six cases of enteric fever. Their one carrier showed temporary sterilization of stools, second case of biliary fistula responded well, while third one failed to improve. Of the six cases of fever, two children showed return of temperature to normal within 48 to 96 hours followed by blood culture becoming sterile; one case showed sterilization of blood but no effect on temperature. Rest of the three cases showed slight effect on temperature curves. They concluded that the effect of aureomycin on typhoid was variable and for the most part could not be interpreted as showing therapeutic effect of drug.

Patel and others[6] (1949) treated four cases with a dose of 0.25 to 1.0 Gm. three hourly. They report that blood culture becomes sterile in 48 to 72 hours, although, clinical improvement is not so striking and takes 7 to 10 days. They report that with aureomycin, course of enteric becomes milder and complications were not seen in their cases.

Woodward, Smadel and Ley[7] (1950) treated four cases of enteric with a dose of 0.5 to 0.75 Gm. four hourly. There were two deaths and poor response in the other two cases. Bailey[1] (1950) reported improvement in peritonitis following typhoid perforation with aureomycin, although the course of fever remained unaffected.

We here give results of aureomycin therapy in 12 cases of enteric fever and the effect of the drug on *B. typhosus* isolated from 16 cases in all *in vitro*.

METHOD OF STUDY

All the patients were accepted for inclusion in investigative series only when adequate clinical and laboratory criteria for diagnosis were satisfied. Of the 12 cases treated in all, 8 cases were in bacteræmic stage when they were taken under observation. Ten cases were of initial attack while two cases were relapses following chloromycetin therapy.

In the majority of cases after administering aureomycin blood culture was done daily till it was found sterile for three successive days. Urine and stool cultures were done on admission, and later on, on alternate days during the 2nd and the 3rd week, till three successive cultures were sterile. Widal was done twice a week.

DOSE AND METHOD OF ADMINISTRATION

All the cases were given, in addition to aureomycin, supportive symptomatic treatment. To prevent oropharyngeal complications vitamin B complex was given in majority of the cases. In seven cases aureomycin was given orally. In one case only intravenously, while in two cases intravenously at the start for a period of six to seven days and later by oral route, while in two cases it was given simultaneously by oral and intravenous routes.

In all the cases an initial loading dose was given and later maintenance dose was continued. The drug was discontinued gradually. Different schedules of treatment were tried to study the effect of variation of dose. In seven cases treated only orally, a loading dose of 1 to 2.5 Gm. of aureomycin was given in 1 or 4 equal doses at 2 hourly intervals. Maintenance dose was given at 4 hourly intervals in 5 cases, and 3 hourly in 2 cases. The amount of maintenance dose given was 40 mg./Kg./day in 1 case, 50 mg./Kg./day in 2 cases, 80 mg./Kg./day in 1 case, 85 mg./Kg./day in 2 cases and 110 mg./Kg./day in 1 case. One case was treated only parenterally with a dose of 100 mg. 6 hourly. Of the four cases treated on combined routes, two were given 100 mg. 6 hourly for a week and later 30-50 mg./Kg./day, while other two cases were given 100 mg. 12 hourly intravenously with 45 mg./Kg./day 6 hourly, orally. Intravenous preparation was given, dissolved in 50 to 100 cc. of saline, slowly in different veins every time. In two cases method of injecting 100 cc. glucose to clean out the syringe and needle before taking it out, was also tried. The cases studied were treated in different weeks of fever. One case was treated in the 2nd week, 6 cases in the 3rd week, 5 cases in the 4th and 5th weeks.

SIDE EFFECTS OF THE DRUG

Oral Preparation :—Side effects were few and negligible except for one case (case 6) who developed moderate vomiting and improved on stopping the drug. No other side effects were observed in the rest.

Intravenous Preparation :—In all the four cases, we observed pain and tenderness at the sites of injections, later resulting in thrombosis of the veins. On case (case 9) had thrombosis of all superficial veins and injections had to be abandoned. Only on three occasions rigors were noted after intravenous injection and were easily contrólled.

SUMMARY OF EACH CASE

(1). Mrs. B. P., aged 22 years, was admitted on 11-7-1950 with a history of continuous fever of 7 days duration and frequency of stools 5-6/day with blood since the last 2 days. The present attack being a relapse of typhoid fever which was treated successfully with chloromycetin; she was alright for a week between two attacks.

Her conjunctivae and mucous membrane of the mouth were pale, nails were pale, tongue was coated in the centre, red blood cell count was 3.8 million, hemoglobin was 58 per cent, while white blood cell count was 5,600. Differential count was within normal limits. Routine examination of stools showed plenty of red blood cells. Urine and stool cultures showed no pathogens. Widal reaction was positive for O and H in 1: 50 dilution. Clot culture was positive for *B. typhosus*.

Patient was given liquid diet consisting of small quantities of apple juice, pomegranate juice and butter milk. Patient was given a blood transfusion of 300 cc. and daily injections of calcium gluconate 10 cc. 10 per cent, coagulen ciba 5 c.c. intramuscularly, vitamin C and glucose 25 per cent and congo red were given. Aureomycin was given on the 34th day with a loading dose of 0.5 Gm. 2 hourly for 4 doses and then 0.5 Gm. 4 hourly. In all 21 Gm. were given in 8 days.

There was little effect on the general condition or temperature. Patient expired on 22-7-1950 from profuse hæmorrhage.

(2). Mr. R. C., aged 22 years, was admitted on 20-7-1950 with remittent fever of 6 days' duration associated with malaise and headache. He complained of frequency of stools 5-6/day of 1 day's duration.

Patient had never been inoculated. On enquiry about the incidence of typhoid in contacts, it was found that the neighbour had fever on the same day while his brother had it 10 months back. On examination, patient looked ill. His tongue was coated in the centre, and margins were red. His pulse was rapid and dicrotic in character. Spleen was 2 fingers below the costal arch. He showed leucopenia of 2,500 with lymphocytosis (44 per cent) and polymorphopenia (54 per cent). His clot culture of 8th day showed pure growth of *B. typhosus*. Widal reactions were positive for O antigen in 1 : 50 dilution. Urine and stool examination both routine and culture showed nothing.

Patient was put on fluid diet measuring about 100 oz. and of total caloric value 1,100. He was given supportive treatment of a diaphoretic mixture, glucose saline subcutaneously, glucose 25 per cent and vitamin C 500 mg. intravenously and

TABLE.—*Showing Summary of Each Case.*

Case No.	Age.	History.	Clinical findings.	Investigation.	Treatment.		Total Dose.	Complications during treatment.	Results.
					Began on	Contd. for			
1	22	Fever—one month. Frequency of stools with blood 2 days.	m.m.—pale, tongue-dry and coated.	W.B.C. 5,600 Clot culture + ve Widal O 1:50 H 1:50	34th day.	8 days.	21 Gm.	....	Expired.
2	22	Fever—6 days Diarrhoea 6 days.	Toxic appearance. Tongue coated. Spleen+2F.	W.B.C. 2,500 Clot culture+ve. Widal O 1:50 Later O 1:1250 H 1:500	11th day.	14 days.	25.75 Gm.	Drowsiness and muttering. Tympanites.	Poor.
3	19	Fever—10 days Vomiting 2 days.	Tongue coated ..	W.B.C. 2,800 Clot culture+ve. Widal H 1:250 O 1:250 A 1:125 B 1: 50	12th day	12 days	40.25 Gm.	Haematemesis Crust on the lips.	Poor Relapse after 7 days.
4	20	Fever—15 days Cough— 3 days.	Toxic appearance. m. m. pale. Tongue coated Liver } +1F Spleen }	W.B.C. 6,900 Clot culture+ve. Widal H 1:500 O 1:500	19th day.	10 days.	24.25 Gm.	Tympanites. ..	Fair.
5	20	Fever with headache 7 days.	Tongue coated ..	W.B.C. 4,500 Clot culture+ve. Widal O 1:250 H 1:250	9th day	23 days.	37.5 Gm.	Cough, Vomiting, Tympanites.	Poor.
6	13	Fever—8 days Drowsiness and muttering—3 days. Diarrhoea 2 days. Cough 3 days.	Toxic appearance. Tongue coated. Tympanites. Lips cracked.	W.B.C. 3,800 Clot— Widal O 1:500 Later O 1:250 H 1:250	11th day	6 days.	25.5 Gm.	Vomiting Bronchial signs.	Poor.

TABLE.—*contd. Showing Summary of Each Case.*

Case No.	Age.	History.	Clinical findings.	Investigation.	Treatment.		Total Dose.	Complications during treatment.	Results.
					Began on	Contd. for			
7	10	Fever—12 days. Muttering and drowsiness—2 days.	Toxic appearance Tongue dry. Liver & spleen+ Crepts. Rt. base.	W.B.C. 2,400 Clot +ve Widal O 1:1250 H 1:500	14th day.	6 days.	15 Gm.	Nil.	Poor. Toxaemia improved. Temperature remained unaffected.
8	50	Fever and headache 15 days.	Tongue coated ..	W.B.C. 4,450 Clot—O Widal H 1:250	17th day.	18 days.	23 Gm. oral 26 inj.	Thrombosis of the veins.	Fair.
9	35	Relapse case. Fever, drowsiness, muttering 3 days.	Toxic appearance. Tongue coated. Skin dehydrated.	W.B.C. 5,000 Clot +ve Widal H 1:500 O 1:250	7th day.	2 days.	8 inj.	Nil.	Fair. Treatment discontinued after 48 hours.
10	35	Fever 13 days. Cough 8 days.	Toxic appearance. Tongue coated. Rose spots on abdomen Liver } 1 F Spleen }	W.B.C. 9,850 Clot- Widal O 1- 50 H 1:125	18th day.	16 days.	32 inj. 13 Gm oral.	Pyelitis Cough and expectoration.	Poor. Toxaemia diminished but no effect on temperature.
11	22	Fever 8 days Pain in rt. hypochondriac region. Cough.	Toxic appearance. Tongue coated. Liver+3F Tender	W.B.C. 7,650 Clot—O Widal H 1:125.	14th day.	7 days.	12.5 Gm. oral.	Nil.	Good.
12	25	Fever Headache } 4 days Cough.	Toxic appearance. Tongue coated. Rt. base—def. air entry.	W.B.C. 5,400 Clot+ve Widal H 1:50 O 1:50	16th day.	10 days.	15 inj. 17 Gm. oral.	Tympanites and cough.	Fair.

vitamin B complex intramuscularly. Aureomycin was started on the 11th day with a loading dose of 2.8 mg./Kg. body weight in 10 hours in five equal doses (*i.e.*, 1.25 Gm.). Maintenance dose was given as 40 mg./Kg. body weight daily in three hourly doses (2 Gm. daily). On the 20th day, the dose was reduced to 34 mg./Kg. body weight daily in 4 hourly doses (1.5 Gm. daily). The drug was omitted on the 25th day, total dose being given was 25.75 Gm. The drug had no effect on the course of the disease.Patient developed tympanites on the 13th day. Patient who showed drowsiness and muttering from the 11th day of illness continued to be so till the 22nd day. Temperature continued fluctuating between 102 and 98 and showed signs of improvement on the 22nd day. Temperature came down to normal on the 24th day, (*i.e.*, 13 days after aureomycin therapy). Pulse showed similar fluctuations. Tongue became clear on the 20th day. Spleen remained palpable till the 24th day of illness. Tympanites started becoming less from the 24th day and disappeared on the 27th day.

Blood culture was negative when examined after 10 days and 18 days. Widal showed increase in titre from 'O'—1: 50 to O 1: 1250—and 'H'—1: 500. Total white cell count had improved to 4,400 when fever had come down. Stool cultures before and after the therapy—in all six—were negative and so were the urine cultures.

Patient was discharged on 16-8-1950.

(3). Mr. M. M. R., aged 19 years, was admitted on 27-7-1950 with a history of remittent fever of 10 days duration with headache of 3 days duration. He complained of 1-2 vomits/day. He was inoculated for T.A.B. 3 years back. Patient gave history of typhoid at home 10 months back.

On examination, tongue was coated in the centre. He showed anæmia. Hæmoglobin was 62 per cent, whereas red blood cell count was 2.9 million. He showed marked leucopenia (2800) with lymphocytosis (53 per cent). Widal reaction was positive in following dilutions—H 1 : 250, O 1 : 250, A 1 : 125, B 1 : 50, while clot culture showed growth of *B. typhosus* and *Staphylococcus aureus*. His routine and cultured stool examination showed nothing particular while urine showed traces of protein, acetones and amorphous phosphates. Urine culture showed *Staphylococcus albus* growth.

Patient was put on liquid diet measuring 125 oz. and valuing 1,500 calories. He was given supportive treatment as follows: A diaphoretic mixture, glucose saline subcutaneously, intravenous glucose 25 per cent with vitamin C 500 mg. and vitamin B complex injections. Patient was given aureomycin on the 31st, *i.e.*, 12th day, at 10 a.m. with a loading dose of 70 mg./Kg. body weight (*i.e.*, 3 Gm. per day) per day. Aureomycin was given in 4 hourly doses as maintenance dose. On 12-8-1950, *i.e.*, 24th day of illness, maintenance dose was further reduced to 42 mg./Kg. body weight in 4 hourly doses per day, (*i.e.*, 1.5 Gm. per day). Total amount of drug was 161 capsules (40.25 Gm.)

The drug had practically no effect on the temperature and pulse. Temperature became normal on the 31st day of illness. Tongue remained coated till the 24th day. Spleen became palpable on the 13th day and remained so for 3 days. Vomiting persisted till the temperature showed signs of decline, (*i.e.*, 25th day). On the 13th and 14th day, he had blood in the vomits but it cleared out with usual coagulant therapy. During the 3rd week, patient showed cracks on lips and crusts on margin of nose, and cleared out by 25th day. Aureomycin was abandoned on 26th day because of poor response. Patient remained afebrile for 7 days. On the 37th day he developed pain all over the abdomen and next day he developed temperature. Blood examination in 2nd week (14th day) showed increase in widal reaction—H 1 : 2,500, O 1 : 1,250, B 1 : 250. Clot culture became negative for *B. typhosus* and remained so in 3rd week also. His urine and stool cultures were repeatedly negative in the 1st, 2nd, and 3rd weeks.

Patient was put on reduced diet during convalescence.

Relapse :—On 38th day patient showed a rise of temperature with tongue red at margins. He developed remittent fever. Tongue became coated in the centre. He developed tympanites on 41st day which subsided after 3 days. His widal test was repeated and showed O 1 : 500, H 1 : 2,500. Clot culture showed pure growth of *B. typhosus.*

Patient was put on chloramphenicol on 5th September, i.e., 48th day, at 12 noon with an initial dose of 4.5 Gm. or 128 mg. /Kg. body weight. In 24 hours maintenance dose of 3 Gm. per day or 85 mg. /Kg. per day in 4 hourly doses was given. With it usual supportive line of treatment was also given. Temperature came down in 48 hours. The maintenance dose was reduced to 1.5 Gm. per day or 42 mg. /Kg' per day on 51st day. Tongue started becoming clear from the next day and became moist and clean in another 48 hours. While bowels which were constipated during pyrexial period started moving normally from 3rd day. On 11-9-1950, *i.e.*, 54th day, maintenance dose was further reduced to 1 Gm. per day or 28 mg. /Kg. per day in 6 hourly doses. Finally, chloramphenicol was abandoned on 14-9-1950, total amount given being 18 Gm. in 8½ days. Patient was discharged on 23-9-1950.

(4). Mr. R. S., aged 20 years, was admitted for continuous fever of 15 days duration associated with malaise and constipation. Patient complained of cough with mucoid expectoration since last 3 days.

On inquiring into previous illness, patient gave history of chronic malaria lasting for six months, 2 years back. Patient was never inoculated with T.A.B. Gave history of typhoid incidence in neighbour, simultaneously.

Patient looked ill. His mucous membrane of conjunctivae and mouth showed pallor. Tongue was dry and diffusely coated. Lips were dry and cracked. He showed fine tremors in all extremities. Liver and spleen were both palpable. Pulse was regular and dicrotic in character. Patient showed a normal red blood cell and white blood cell count; differential count revealed polymorphs 58 per cent, lymphocytes 37 per cent, monocytes 2 per cent, eosinophils 3 per cent. Widal was positive for H. and O, both in 1 : 500 dilution. Clot culture showed pure growth of *B. typhosus.* Urine showed few epithelial cells and pus cells but cultural examination did not show any growth. Stool culture was also negative.

Patient was put on fluid diet measuring about 120 oz. and total caloric value of 1,300. He was given supportive treatment of diaphoretic mixture, glucose 25 per cent 100 c.c. with vitamin C 500 mg., glucose saline S. C. and vitamin B complex intramuscularly. Aureomycin was started on 19th day with a loading dose of 40 mg. per Kg. body weight in first 10 hours in five equal doses at two hourly intervals, (*i.e.*, 2.5 Gm. in 10 hours). Later 40 mg. /Kg. was given in next 15 hours in 3 hourly doses. Maintenance dose was given as 50 mg. /Kg. body weight in 24 hours in four hourly doses. Aureomycin had beneficial effect on the course of illness.

From the 2nd day of aureomycin therapy, fever showed less than usual fluctuations. Whereas, before treatment fluctuations ranged between 102.5 and 98, it now showed fluctuations between 101.5 and 99. Within 4 days it further dropped to 99.5 and 97. Fever touched normal on 29th day of illness, *i.e.*, 10 days after aureomycin was given. Pulse and respiration rate showed corresponding variations and came to normal limit with temperature.

On the day of starting aureomycin, patient showed muttering which cleared up in next 2 days. Tongue showed improvement from 24th day of illness and was clear on 29th day. Lips remained dry and crusted till 22nd day. Patient developed tympanites on 20th day and got rid of it on 29th day. Liver and spleen remained palpable till 25th day.

After a week clot culture had become negative for *B. typhosus*, stool cultures on alternate days were negative and so were urine cultures. Widal showed little change.

Patient was given in all 24.25 Gm. of aureomycin. He was discharged cured on 28-8-1950.

(5). Miss N. J., aged 11 years, was admitted on 21-8-1950 with 7 days remittent fever accompanied with headache, malaise and constipation and occasional vomiting. On examination, tongue was found coated and dry. Her blood examination showed hæmoglobin 85 per cent, red blood cell 4.1 million, white blood cell 4,500 while differential count showed polmorphs 68 per cent, lymphocytes 30 per cent, eosinophils 2 per cent. Widal was positive for O and H. antigens in 1 : 250 dilutions. Clot culture showed pure growth of *B. typhosus.* Routine and cultural examination of urine and stool showed nothing abnormal.

Patient was put on liquid diet measuring 110 oz. and valuing 1,300 calories. She was given supportive treatment of a diaphoretic mixture, glucose saline subcutaneously 100 c.c., 25 per cent glucose with vitamin C 500 mg. intravenously and vitamin B complex intramuscularly on alternate days. Aureomycin was started on 23rd, *i.e.*, 9th day at 6 p.m. with a loading dose of 35 mg./Kg. in a single dose (*i.e.*, 1Gm) and maintenance dose was given as 110 mg./Kg. per day in four hourly dcses. On 29th day, *i.e.*, 15th day of fever, maintenance dose was reduced to 55 mg./Kg. body weight per day in four hourly dosage. On 9-9-1950, *i.e.*, 25th day of illness when fever had come down to normal, aureomycin was further reduced to 37 mg./Kg. per day in 6 hourly doses. Drug was stopped on 7th day after fever touched base line, total amount of drug given being 150 capsules, *i.e.*, 37.5 Gm.

Drug showed no beneficial effect in fever or general condition. It remained fluctuating for 14 days and became normal on 22nd day of illness. Coating and dryness of the tongue became clear after fever came down *i.e.*, on 27th day of illness. Vomiting continued during the whole period of illness, 1-21 days, and stopped immediately the drug was discontinued. Patient developed slight cough with expectoration on 12th day and tympanites on 14th day. Tympanites remained for 4 days while cough persisted for the whole period of pyrexia.

Clot culture remained positive for 3 days after aureomycin was started. Repeated examinations of urine and stool cultures in 2nd week were all negative while widal became strongly positive (H : 250, O 1 : 500) in 2nd week.

Patient was discharged on 15-9-1950.

(6). Miss V., aged 13 years, was admitted with remittent fever of 8 days duration, drowsiness and muttering of 3 days duration. She had frequency of stools 2-3/day and cough with expectoration of 2 days duration. Patient gave history of typhoid in family 4 years back. On examination, tongue was dry and coated, lips were dry and cracked. She showed generalised tremors and tympanites. Her blood examination revealed red blood cell 4 million, hæmoglobin 81 per cent, white blood cell 3,800, with lymphocytes 38 per cent, polymorphs 60 per cent and monocytes 2 per cent. Widal was positive in 1 : 500 dilution for O antigen. Clot culture was negative for *B. typhosus*, and stool routine and cultural showed nothing abnormal.

Patient was given liquid diet measuring 110 oz. and valuing 900 calories. She was also given supportive and symptomatic treatment. A diaphoretic and sedative cough mixture, glucose saline intravenously, glucose with vitamin C and vitamin B complex and folic acid were given. Patient was put on aureomycin on 30/8, *i.e.*, 11th day at 8 p.m. with an initial dose of 1 Gm. Maintenance dose of 85mg./Kg. body weight per day in 4 hourly doses (*i.e.*, 3 Gm./day) was given. On 4/9, *i.e.*, 16th day of illness, aureomycin dose was doubled thinking that the dose was too small, total aureomycin given being 120 caps., 25.5 Gm. On 6/9, *i.e.*, 18th day chloromycetin was given in the following dose. Initial dose was 70 mg./Kg. body weight or 2.5 Gm. in 10 hours in two hourly doses. In next 15 hours similar dose was given in three hourly doses. Maintenance dose of 85 mg./Kg. body weight per day in 4 hourly doses. On 11/9, *i.e.*, 23rd day, chloromycetin was reduced to 42 mg./Kg. per day in 4 hourly doses. On 13/9, *i.e.*, 25th day, it was further reduced to 28 mg./Kg. day in 6 hourly doses. It was abandoned on 28th day.

The drug had little effect on fever or general course of illness or complications. On admission, patient developed retention of urine which continued for 4-5 days. Tympanites increased and remained so during the whole period. Temperature kept on fluctuating while patient showed marked toxicity and delerium during the whole pyrexial period. She had disturbed sleep during this time. Patient became slightly dyspnoeic on 3/9, *i.e.*, 15th day. On 3rd she developed bronchitis, On 4th day both the lungs showed bubbling rales. On 1/9, *i.e.*, 13th day, patient had diarrhœa 3-5/day, while from 4/9, *i.e.*, 16th day, she had 1-2 vomits per day.

Clot culture was negative in 1st and 2nd week while stool and urine cultures were negative on 1st, 2nd and 3rd week. Widal showed increase in concentration in the next week, H. 1 : 250, O 1 : 250.

On 6/9, *i.e.*, 18th day, chloromycetin was given, within 48 hours patient showed improvement in toxicity. She became more alert, stopped muttering and slept well at night. Within next 24 hours, lips and tongue became clear. While dyspnoea became less, diarrhœa stopped. Temperature came to normal after 156 hours. Lungs became clear after 96 hours. Temperature, though reduced, took 7 days to be normal. Patient developed a subcutaneous abscess at an injection site which was treated with penicillin and fomentations. She was discharged on 20-9-1950.

(7). Miss S., aged 10 years, was admitted on 23-9-1950 with a history of continuous fever of 12 days duration and muttering and drowsiness of 2 days duration.

On examination, patient was poorly nourished and looked ill and toxic. Her tongue was dry and coated. Her lips were dry and cracked. Both liver and spleen were palpable. There were crepitations at right base. Soft systolic murmur was heard at apex.

On investigation, red blood cell count was 2.7 million, hæmoglobin was 52 per cent, while white blood cell was 2.450 with a differential count showing polymorphs 51 per cent, lymphocytes 47 per cent, eosinophils 2 per cent. Widal reaction was positive for H and O antigens in 1 : 500 and 1: 1250 dilution, respectively. Routine and cultural examination of urine and stool were normal. Blood culture showed pure growth of *B. typhosus*.

Patient was put on fluid diet of 120 oz. a day amounting to 1,200 calories and she was given supportive lines of treatment in the form of a diaphoretic mixture, a pint of glucose-saline subcutaneously and glucose and vitamin C intravenously, vitamin B complex and folic acid injections. Patient was given aureomycin 80 mg./Kg. body weight/day by mouth in 3 hourly doses, starting on 14th day. The drug was abandoned on 28th day of illness. Chloromycetin was started on 40th day with a dose of 60 mg./Kg. body weight/day in 4 hourly doses. On the next day it was further reduced to 20 mg./Kg. body weight/day in 4 hourly doses. Drug was stopped on the next day. Total amount given was 15 Gm. in 6 days. Aureomycin had little beneficial effect on temperature or pulse. On 6th day of therapy, signs of toxaemia became markedly less; patient became alert. Tongue, liver and spleen remained the same throughout illness. Drug was abandoned after 14 days, when 41.75 Gm. were tried. With chloromycetin, temperature came down by lysis in 60 hours. Pulse and respiration also became normal by that time. Tongue became clear in next 4 days, while liver and spleen shrunk to normal size in 2 days. Patient was discharged on 28-10-1950.

(8). Mr. A. R., aged 50 years, was admitted to the hospital with a history of fever of 15 days duration and hectic in nature with slight headache. On examination, tongue was coated and dry.

On investigation, red blood cell count was 4.2 million while hæmoglobin was 88 per cent. White blood cell count was 4,450 with polymorphs 61 per cent, lymphocytes 38 per cent, and eosinophils 1 per cent. Urine showed traces of sugar and few pus cells. Culture of urine, stool, and blood were negative for *B. typhosus.* Widal reaction was positive for H. antigen in 1 : 250 titre.

Patient was put on liquid diet of 130 oz. with a caloric value of 1,700 calories. He was given a diaphoretic mixture, glucose-saline subcutaneously and glucose with vitamin C intravenously, folic acid and B complex intramuscularly. Patient was given 100 mg. of aureomycin intravenously every 6 hours starting on 17th day. Injections were replaced by oral aureomycin on 24th day with a dose of 50 mg./Kg. body weight/day. Later, on 27th day, it was reduced to 32 mg./Kg. body weight/day, on 28th day to 25 mg. and finally on 30th day to 15 mg./Kg. body weight. The drug was stopped on 35th day, total amount given being 26 injections and 23 Gm. orally. With intravenous aureomycin, patient showed gradual fall in temperature and control in range of daily variations in 72 hours. After 96 hours, temperature fluctuated between 100 and 97 and reached normal after 9 days treatment. Tongue became clear and moist within 4 days treatment. Patient developed thrombophlebitis of the vein of the dorsal carpal arch on 25th day, *i.e.*, on 7th day of intravenous medication, which subsided in a week's time.

Blood, urine, and stool cultures were repeatedly negative in 2nd week. Patient was discharged on 30-10-1950.

(9). Mr. U. J., aged 35 years, cleaner by occupation, was admitted on 15-9-1950 with a history of 10 days continuous fever with cough and expectoration and pain in the chest.

On examination, patient showed dry and coated tongue, rhonchi scattered all over and distended abdomen. On investigation, there was normal blood count while widal reaction showed B 1 : 50, and O 1 : 250.

Patient was treated on usual supportive line of treatment and chloromycetin with a dose of 2 capsules 4 hourly. In all he was given 12 Gm. Temperature came down in 120 hours while general condition improved in 80 hours. He remained normal for 10 days and developed a relapse. His widal reaction showed H 1 : 500, O 1 : 250, while blood culture showed pure growth of *B. typhosus.* On 3rd day he became markedly toxic. He was put on usual lines of supportive therapy and intravenous aureomycin with a dose of 100 mg. four times a day. From next day he showed improvement in temperature, but on 4th day he developed pain at the sites of intravenous injections and all the superficial veins were found to be thrombosed. The drug had to be abandoned because of this. Total amount given being 800 mg. intravenously.

Patient recovered after a fortnight.

(10). Mr. C. K., aged 35, was admitted on 13-11-50 with a history of continuous fever since last 13 days and dry cough since last 8 days.

On examination, patient was found toxic. Tongue was dry and coated. There were rose spots on the abdomen and chest. Liver and spleen were just palpable. Occasional rhonchi were heard over the chest.

On investigation, hæmoglobin was 80 per cent, red blood cell 4.02 million, white blood cell 9,850. Differential count was within normal limits. Urine showed traces of albumin and occasional pus cells. Stool examination did not show anything abnormal. Blood, urine and stool cultures were sterile. Widal showed O 1 : 50

which on 3rd day became positive in 1 : 125 dilution. On 26th day, patient showed 30-40 pus cells in urine with traces of albumin. Culture failed to grow organisms.

Patient was put on liquid diet of 110 oz. amounting to 1,500 C. Patient was given a diaphoretic mixture, glucose saline 1 pint subcutaneously and glucose 25 per cent. 100 c.c. with 500 mg. vitamin C intravenously. On 18th day, aureomycin 100 mg. was given intravenously four times a day. Injections were replaced by oral treatment after a week, the dose given being 33 mg/Kg/day in four hourly doses. Aureomycin was abandoned on 34th day. Total amount given intravenously was 32 injections and orally 13 Gm.

Patient showed improvement in general condition with aureomycin treatment. His toxicity became less. There was nc effect on temperature, pulse or respiration. Tongue remained same. Liver and spleen disappeared on 25th day. On 19th day, patient developed cough with expectoration and showed moist sounds in both lungs. Cough and lung signs cleared out in 5 days.

Four consecutive blood cultures in 2nd week were negative for *B. typhosus*. Repeated cultural examination of stools and urine during 2nd week failed to show organisms.

On 26th day, patient developed burning urine and there was a further rise in range of temperature. Urine examination showed traces of albumin and 30-40 pus cells/field; culture failed to detect organisms. Patient was put, in addition to aureomycin, on penicillin with a dose of 1 lac 4 hourly. Symptomatic relief was obtained in 8 days. Urine became clear in 12 days time.

Temperature came down on 34th day. Pulse and respiration improved. Simultaneously, tongue became clear and moist. Patient was discharged on 22-12-1950.

(11). Mr. M., aged 22 years, was admitted to the hospital on 14-12-1950 with a history of continuous fever of 8 days duration accompanied by pain in the right hypochondrium. Pain was aggravated on coughing and deep inspiration. Patient was constipated. Since last 4 days, he had slight cough with mucoid expectoration.

Patient gave history of an attack of dysentery 1½ months back.

On examination, tongue was coated. Tonsils were slightly enlarged but were not congested. There was fullness in the right hypochondrium due to enlarged left lobe of the liver for 3 fingers below costal arch. It was tender. There was tenderness in right iliac fossa. Base of right lung showed diminished movement and air entry.

On investigation, hæmoglobin was 60 per cent, red blood cell 2.9 million while white blood cells was 7,650. Differential count was polymorphs 62 per cent, lymphocytes 34 per cent, monocytes 2 per cent, eosinophils 2 per cent. Routine examination of urine did not show anything abnormal. Stools showed occasional vegetative forms of *G. lamblia*. Icterus index was 8 units. Van den Bergh's test was indirect positive. E. S. R. was 1 mm. at end of 1 hour by Wintrobe's method. Widal reaction showed agglutination against H antigen in 1 : 125 dilution. Blood, urine and stool cultures did not show growth of *B. typhosus*.

Patient was given a diaphoretic mixture and glucose 25 per cent 100 c.c. intravenously. He was put on liquid diet of 100 oz. having 1,500 caloric value. On 14th day, aureomycin was started. Patient was given injections of aureomycin 100 mg. morning and evening. He was given orally 45 mg. of aureomycin per Kg. of body weight per day in 6 hourly doses. On 19th day, oral dose of aureomycin was reduced to 34 mg./Kg./day; on the following day injections were discontinued and oral dose was further reduced to 22 mg./Kg./day. Aureomycin was stopped on 21st day of illness. Total dose given was 12.5 Gm.

Treatment with aureomycin had beneficial effect on the course of disease. Temperature became normal by lysis in 36 hours. Pulse and respiration showed simultaneous improvement. Tenderness of liver area disappeared in 2 days. Liver remained enlarged for a week and then gradually subsided in 4 days time. Tongue became clear and moist in 4 days. Lungs became normal in 8 days. Patient showed thrombosis of superficial veins in which aureomycin intravenously was given.

Three consecutive culture examinations of blood were negative for *B. typhosus*, while repeated examinations of urine and stool did not show any growth. Widal reaction remained the same in the 3rd and 4th week.

Patient was discharged on 1-1-1951.

(12). Mr. K., aged 25 years, was admitted on 24-12-1950 for continuous fever with frontal headache and dry cough of 4 days duration.

On examination, tongue was coated. There was impaired note at right base with deficient air entry.

On investigation, red blood cell was 4.2 million, hæmoglobin 82 per cent, white blood cell 5,400. Differential count was within normal limits. Widal reaction was positive for H and O antigens in 1 : 250, and 1 in 125 titre, respectively. On 16th day, widal showed H 1 : 250, O 1 : 500. Clot culture showed pure growth of *B. typhosus*. Routine and cultural examination of urine and stools were normal.

Patient was put on fluid diet containing 100 oz. and estimating 1,500 calories. He was given a diaphoretic mixture and glucose saline 1 pint subcutaneously. He was put on aureomycin on 16th day. He was given 100 mg. aureomycin twice intravenously with 40 mg. /Kg. per day orally in 6 hourly doses. Injections were discontinued on 23rd day of illness. Aureomycin was reduced to 20 mg. /Kg. per day in 6 hourly doses on 23rd day. Finally, it was abandoned on 15th, i.e., 27th day of illness, total amount given being 15 injections and 17 Gm. by mouth.

Patient showed improvement with the treatment. In the beginning of treatment he developed tympanites (on 17th day) and rhonchi were heard (on 17th day) and had frequency of stools (on 18th day). But there was an overall improvement from 19th day. Toxicity started subsiding. Temperature came down by lysis on 23rd day. Pulse and respiration accompanied the temperature. His tongue cleared. Tympanites and diarrhœa disappeared.

Clot culture was negative for *B. typhosus* at the beginning and during the treatment. Urine and stool cultures during treatment were negative. Patient was discharged on 20-1-1951.

RESULTS

1. *Overall response to the drug* :—There was no dramatic improvement in any of the cases; however, fair response was observed in five cases. General condition improved in 24 to 72 hours. The toxæmia became less, temperature fluctuations less, and temperature returned to normal in 1½ to 9 days after therapy. Two cases showed improvement in general condition but no improvement in temperature. One case admitted with hæmorrhage expired, while in two cases condition continued to deteriorate and chloromycetin had to be resorted to. The remaining two cases continued unaffected and ran through the normal course.

2. *Effect on temperature* :—In five successful cases, fluctuations were under control within 24 to 72 hours of treatment, except in one case where it took 128 hours. Case 11 showed return of temperature

to normal in 36 hours, in three cases temperature fell by lysis in 8 to 10 days.

3. *Effect on Toxæmia* :—Of the 12 cases, 8 cases showed signs of severe toxæmia at the onset of treatment. Of these, seven cases showed improvement while only one remained unaffected. The remaining four cases showed mild or moderate toxæmia and remained unaffected. When effective, toxæmia was under control in 48 to 72 hours though for its complete disappearance, 6 to 13 days were required.

4. *Effects on signs and symptoms* :—In most of the cases physical signs cleared after the temperature returned to normal. There was symptomatic improvement *pari passu* with improvement in general condition and fever.

5. *Development of complications* :—In this series of patients treated with aureomycin no major complications devleoped during treatment. Four cases had tympanites, one had transitory hæmatemesis for two days, three cases developed bronchial signs and catarrh, while one case showed crust on the lips. Case 1 is not included as treatment was given after hæmorrhages had occurred.

6. *Relapses* :—Only one case showed a relapse, after seven days of temperature coming to normal. Relapse was successfully treated with chloromycetin.

7. *Mortality* :—One case died. That was No. 1 She was admitted with melæna and expired after 8 days of treatment.

8. *Effect on blood culture* :—At the onset of treatment 8 patients showed positive clot culture. Three cases were treated during bacteræmic stages. Clot cultures became negative as follows :—

TABLE 1.—*Time Taken for Blood Cultures to be Negative*

Case No.	Hours.	Average.
9	48	72 hours.
7	72	
5	96	

9. *Effect on stool and urine cultures* :—Stool and urine cultures were repeatedly negative during treatment in all the cases.

10. *Effect on Widal reactions* :—In all the cases in this series, widal remained same or increasing titres were obtained during the course of treatment. No definite co-relation of widal to treatment could be derived.

11. *Effect of severity of illness and duration of symptoms before treatment on response* :—

It seems that drug has effect on moderate as well as severe cases. The greater number of fair response in severe cases is explained by beneficial effect of aureomycin on toxæmia. We have not been able to study early cases where it may be more effective.

TABLE 2.—*Relationship of Severity of Illness, and Duration of Symptoms Before Treatment with Response*

Days of symptoms before treatment.	Severity of illness.	Number of cases.	Average days of pyrexia to return to normal.	Overall Response.
7-14 days.	Moderate	3	..	poor.
	Severe	5	1 case 36 hours 1 case not determined.	2 good 3 poor.
15-21 days	Moderate	1	10 days.	fair.
	Severe	3	8 days.	2 cases fair 1 case poor.
22-25 days	Severe	1	..	expired.

12. *Effect of frequency, amount and route of treatment on response.* Table 3 is self-explanatory.

TABLE 3.—*Relationship of Effect of Frequency, Amount and Route of Administration with Response*

Method of administration.	Maintenance dose per day.	Frequency	Number of Cases.	Response.
Orally	40 mg./Kg. body wt.	3 hourly	1	Poor.
	50 mg./Kg. ,,	4 hourly	2	Fair in case
	80 mg./Kg. ,,	3 hourly	1	Poor.
	85 mg./Kg. ,,	4 hourly	2	Poor.
	110 mg./Kg. ,,	4 hourly	1	Poor.
Parenterally I. V.	400 mg.	6 hourly	1	Fair.
Combined. I. V. followed by oral.	400 mg. for 7 days	6 hourly	2	Fair.
	30-50 mg./Kg. later on	6 hourly		
Oral and I.V. together	200 mg.	12 hourly	2	Fair.
	45 mg./Kg.	6 hourly		

13. *Aureomycin sensitivity in vitro* :—In all 13 samples of *B. typhosus* isolated from the cases were studied by turbidimetric method. Cultures were prepared in broth and serial dilutions of drugs were added. Results were taken after 24 hours. 209 *P. Staph aureus* was kept as a control.

TABLE 4.—*Showing Aureomycin Sensitivity in Vitro.*

Serial No.	Case No.	Concentration of aureomycin per c.c. of broth:							
		160 mgm. cc.	80 mgm. cc.	40 mgm. cc.	20 mgm. cc.	10 mgm. cc.	5 mgm. cc.	2.5 mgm. cc.	nil.
Control	209 P. Staph. aureus.	–	–	–	–	–	–	,,	,,
1	IV	–	slight	,,	,,	,,	,,	,,	,,
2	V	–	–	,,	,,	,,	,,	,,	,,
3	VII	–	–	,,	,,	,,	,,	,,	,,
4	III	–	–	,,	,,	,,	,,	,,	,,
5	IX	–	–	,,	,,	,,	,,	,,	,,
6	XII	–	–	slight	,,	,,	,,	,,	,,
7	*	–	slight	,,	,,	,,	,,	,,	,,
8	*	–	–	slight	,,	,,	,,	,,	,,
9	*	–	–	–	slight	,,	,,	,,	,,
10	*	–	–	,,	,,				
11	*	–	–	slight	,,	,,	,,	,,	,,
12	*	–	–	,,	,,	,,	,,	,,	,,
13	*	–	–	,,	,,	,,	,,	,,	,,
14	*	–	–	slight	,,	,,	,,	,,	,,
15	*	–	–	,,	,,	,,	,,	,,	,,
16	*	–	–	,,	,,	,,	,,	,,	,,

* Cultures isolated from cases which are not included in aureomycin trial series.

,, Turbidity indicating growth.

– No turbidity. Inhibition of growth.

Slight—Slight turbidity.

N.B.—We have sent samples of these 16 cultures to U.S.A for typing purposes, the report of which will be communicated in another article.

COMMENTS

Effect of aureomycin therapy in typhoid is variable. There was an overall favourable response in 41 per cent (5 cases) of cases treated. Of these, four cases showed severe toxæmia, while one showed moderate. It seems that the drug has beneficial effect on the course of the disease. Toxæmia improved in 87 per cent of the cases, *i.e.*, of the 8 cases of severe toxæmia, 7 showed definite improvement in toxæmia in 48 to 72 hours. In all these cases complete amelioration of toxæmia required 6 to 13 days. Of these 7, in 2 cases temperature failed to respond in spite of marked reduction in toxicity. One case of severe toxæmia (13 per cent) continued unabated. In two cases (case nos. 6 and 7, chloromycetin had to be given. The average duration in which temperature became normal varied much in these six cases. Temperature range was within control in 24 to 72 hours while it became normal by lysis in 8 to 10 days. With relief of toxæmia and fever, other symptoms improved and signs cleared out. In three successful cases blood culture became sterile within 48 to 96 hours.

Seven cases (59 per cent) failed to show overall favourable response. Of these, 3 showed severe toxæmia while three showed moderate toxæmia. One case admitted with hæmorrhages expired while the remaining five cases ran through their usual course.

The striking feature in these 12 cases was absence of any major complications. During treatment minor complications like bronchitis, tympanites, etc., were occasionally seen. As compared to the high incidence of relapse in untreated cases and those treated with chloromycetin, the relapse rate seems to be much less (8.5 per cent). In our series, we had only one relapse.

Parenteral mode of administration was found to be more effective. In all the five cases so treated, there was a good response, but local reactions at the sites of injections must be carefully watched. Combined intravenous and oral treatment may be more effective than oral treatment alone.

We find that the average concentration of aureomycin required to inhibit growth *in vitro* experiments was 80 mg. per c.c.

Side effects of oral preparation were few and negligible. Tenderness at the site of injection and thrombosis of the vein were common when repeated intravenous injections were given.

We believe that a short combined therapy of 100 mg. aureomycin intravenously twice a day and 2-3 Gm. by mouth a day in divided doses for a short period till toxæmia is under control, followed by oral therapy, will give good results with least danger of thrombophlebitis.

Though the number of cases is small, the beneficial effect of aureomycin on toxæmia and course of illness is evident. Further work on relapse rate and carrier rate is indicated. In combination with chloromycetin, there might be much less incidence of relapses, and the problem is under investigation.

SUMMARY

Literature on results of aureomycin therapy in enteric fever is reviewed. Report on results of twelve cases of enteric fever treated with either oral or parenteral or by combined therapy are reported. Sensitivity test on 16 specimens of *B. typhosus* is also reported.

It is considered that the drug has a variable effect. In a good number of cases there was a beneficial effect on the course of the disease and the toxæmia. Further work on the complication rate, carrier rate, and relapse rate is indicated.

We are indebted to Lederle Laboratories (India) Ltd., for the free supply of the drug and other facilities offered by them and to Dr. P. M. Sangani, Superintendent of the Sir Hurkisondas Nurrotumdas Hospital and Dr. Mankad, Head of the Pathology Department for giving facilities to enable us to carry out this study.

REFERENCES

1. Bailey, C. A. and Jumeaux, C. V.: Aureomycin in Treatment of Peritonitis, B. M. J. **1** : 271-273, 1950.
2. Brainerd, H., Clerk, W. H. and others : The Clinical Evaluation of Aureomycin, J. Clin. Invest. **28** : 993-1005, 1949.
3. Bryer, M. S., Schoenbach, E. B., Candler, C. A., Bliss, E. A. and Long, P. H.: Aureomycin, Experimental and Clinical Investigations, J. A. M. A. **138** : 117-119, 1948.
4. Finland, M., Collins, H. S. and Paine, T. C. Jr.: Aureomycin, A New Antibiotic, J. A. M. A., **138** : 946-949, 1948.
5. Knight, V., McDermott, W., and Ruiz-Sanches, F.: Aureomycin and Chloramphenicol, Use in Typhus, Typhoid and Brucellosis, J. Clin. Invest. **28** : 1052-1053, 1949.
6. Patel, J. C. and others : Aureomycin in Typhoid Fevers, Indian Medical Gazette, **84** : 497-500, 1949.
7. Woodward, T. E., Smadel, J. E. and Ley, H. L. Jr.: Chloramphenicol and other Antibiotics in the Treatment of Typhoid and Typhoid Carriers, J. Clin. Invest. **29** : 87-99, 1950.

ANTI-COAGULANTS IN HEART DISEASES

K. K. Datey *

Thrombo-embolic complications are among the more serious threats that terminate the life of a decompensated cardiac patient, and therefore, some means of combating these phenomena are a very pressing need in cardio-vascular therapeutics.

The statistical data collected in recent years has shown conclusively that thrombo-embolic phenomena occur frequently with congestive heart failure and possibly with greater frequency with this condition than with any other single disease. Hines and Hunt[35] detected gross pulmonary infarts in 34 per cent of their 234 cardiac cases at autopsy. Hampton and Castleman[32] in a series of 370 cases of pulmonary embolism and infarction at autopsy noted that 29 per cent were cardiac cases. Kinsey and White[49] reviewed 200 cases of congestive cardiac failure and found an incidence of pulmonary infarction in 40 per cent of their 45 autopsied cases. Similarly, Greenstein[31] detected the incidence of pulmonary emboli in 50 per cent of his 32 cardiac cases at autopsy.

The incidence of mural thrombi in the heart is particularly high in cases of myocardial infarction. Wolff and White[88] detected mural thrombi in 30 per cent of their post-mortem cases of myocardial infarction. Levine and Brown[51] noted mural thrombi in 83 per cent of their cases of myocardial infarction. More recently, Nay and Barnes [64] have reported thrombo-embolic complications in 37 per cent of their 100 cases convalescing from acute coronary occlusion. Hallerstein and Martin[34] in a post-mortem study of 160 cases of acute coronary occlusion found intra-cardiac mural thrombi in 41 per cent of the cases. Thrombo-embolic lesions were the chief cause of death in 15 per cent of the cases and a contributory cause in an additional 12 per cent. Garvin[26] found mural thrombi in the hearts of 67 per cent of patients dying of acute myocardial infarction. Wright[92] in his latest report on 1031 cases of myocardial infarction detected 41.8 thrombo-embolic complications per hundred cases.

These and many other reports give convincing evidence that the incidence of thrombo-embolic complications is high in cases of congestive cardiac failure and particularly so in cases of myocardial infarction.

MECHANISM OF CLOTTING

For a proper understanding of the thrombo-embolic phenomena, we must consider the mechanism of intravascular and intramural clotting. As far back as 1904, Morawitz[60], Fuld and Spiro[25] had established the main steps in the process of clotting. However, recent investigators[23] have postulated a number of accessory factors and reactions that take part in the clotting mechanism.

---

*Bombay Hospital.

The first step in intra-vascular clotting commences with the adhesion of platelets to the intima of a blood vessel often at a point where the endothelium has been damaged. This collection of platelets—called the 'white thrombus' because of its colour, serves as a nidus for a true fibrin clot. Some of these platelets disintegrate and release a material[79] which acts in conjunction with thromboplastin, which in the presence of ionised calcium, converts inactive prothrombin to active thrombin. This thrombin transforms another protein, plasma accelerator globulin, to serum accelerator globulin, which in turn greatly accelerates the rate of thrombin formation[80]. This thrombin when in sufficient quantity converts fibrinogen to fibrin. The network of strands of fibrin extend out into the blood stream and entraps not only platelets but also leukocytes and erythrocytes, and the vessel soon gets occluded by a typical red clot.

CAUSES OF THROMBOSIS

Coagulation of blood *in vivo* results from a disturbance of equilibrium between the anticoagulant and coagulant factors normally present in the fluid plasma. If the local production of thrombin is greater than the rate at which it is being neutralised by antithrombin in the plasma, clotting is likely to occur. The concentration of thrombin sufficient to produce clotting is largely determined by the conditions of blood flow. Rapid blood flow will cause the thrombin to be diluted in the general circulation with subsequent inactivation, while with local stasis the concentration of thrombin is high and conduces to massive coagulation. The conditions of blood flow, therefore, are of paramount importance in the incidence of phlebothrombosis.

The most important single cause that predisposes to thrombosis of leg veins is the sudden confinement to bed of a previously ambulant patient[40]. The diminished use of leg muscles, the absence of deep breathing, dehydration and long hours of quiet due to excessive sedation, predispose to venous stasis and subsequent thrombosis.

Similarly, the stasis of blood in the cardiac chambers is conducive to thrombus formation, particularly so, when there is damage to the endocardium and when myocardial contraction is not co-ordinated as occurs in auricular fibrillation and myocardial infarction.

VENOUS THROMBOSIS

By means of phlebography Bauer[4] has shown that venous thrombosis almost always commences in the deep veins of the calf muscles, and only in about 3 per cent of the cases in the thigh or the pelvis.

As noted previously the nidus of the thrombus is white, the body is dark and firm, and it may grow for a considerable distance towards and away from the heart. The tail that extends from the body is more and more clot-like—red, soft and friable, until it can hardly be distinguished from normal blood. The extension of the clot away from the heart, merely blocks more of the peripheral venous tree. But as the clot extends towards the heart, becoming a slippery, "eel-like formation, 40 to 50 cm. long," unfixed and wavering freely, it hangs like the "Sword of Damocles," ready to be torn free and become an embolus which may prove fatal.

CLINICAL FEATURES

The clinical features of thrombo-embolic complications consist of:—

(*i*) Venous thrombosis,

(*ii*) (*a*) Arterial and (*b*) Pulmonary embolism.

(*i*) *Venous thrombosis* :—For the successful treatment of venous thrombosis, early diagnosis is essential and this is only possible if physicians are 'thrombosis' conscious.

The presence of unexplained tachycardia or fever in a patient confined to bed should arouse the suspicions of the physician and should lead to a thorough examination of the legs. During the early stages of venous thrombosis in the deep calf muscles, the signs and symptoms are minimal and the physician has to use all his resources and ingenuity to diagnose this condition.

The patient may only complain of slight pain or cramp in his calf muscles. Physical examination may reveal engorgement of superficial veins on one side or slight swelling of the affected leg. The calf muscles should be palpated with the patient lying on his back, with his knees half flexed and the soles of his feet, flat on the mattress—thus relaxing the calf muscles. Firm palpation may reveal a tender area or a local induration of the calf muscles. Similarly, the plantar, adductor and femoral regions should be examined for local tenderness. And finally 'Homan's Sign'[36] should be elicited by dorsiflexing the foot on an extended knee. In the presence of deep calf thrombosis, pain in the calf muscles is felt.

(*ii*) (*a*) *Arterial embolism* :—Arterial emboli usually arise from thrombi in the left side of the heart. Their manifestations will depend on the site of infarction—in the brain, the viscera or the limbs.

(*ii*) (*b*) *Pulmonary embolism* :—Pulmonary emboli which commonly complicate heart diseases usually arise from thrombi in the veins of the lower extremities and occasionally only in the right ventricle[50].

The diagnosis of pulmonary embolism is relatively simple when a patient with venous thrombosis in the legs, develops sudden chest pain or hæmoptysis. Fever, tachycardia, hæmoptysis, pleurisy and signs of consolidation in the lungs may suggest the diagnosis. However, in many cases, the primary cardiac or respiratory condition often obscures the true nature of the disease. Sagall[77] and his associates in an analysis of 108 cases of pulmonary embolism, have shown, that the clinical pictures had mimicked in a large number of cases myocardial infarction, angina pectoris, pneumonia, pleurisy, vascular collapse and acute cardiac failure.

It is imperative to make an early diagnosis of pulmonary embolism. If the first warning of embolism is unheeded, fatal embolism may occur, before effective treatment is instituted.

PREVENTION OF THROMBOSIS

From an earlier discussion it is clear that venous stagnation is a very important factor which predisposes to thrombosis and subsequent thrombo-embolic phenomena. Elevation of the legs and active leg exercises, whenever possible, will prevent to some extent, the stagnation of blood and thus lessen the incidence of venous thrombosis. However, this is not possible in acutely ill cardiac patients, and therefore, the most logical and effective way to combat this condition is by preventing the formation of thrombi by the routine use of anti-coagulants. Anti-coagulants do not dissolve the thrombi and therefore their greatest value lies in commencing their use early.

Anti-coagulants: the two anti-coagulants in common use are heparin and dicumarol.

HEPARIN

Heparin was discovered, as a by-product of another investigation, in 1916 by McLean[58], a second year student working in Howell's Laboratory at the Johns Hopkins University.

It was named heparin as it is present in a comparatively high concentration in the liver. As far back as 1917, Howell[37] expressed the hope that heparin would be used in the therapeutic treatment of the disorders of coagulation. Considerable work on this subject was carried out by Howell[38,39], Charles [15], Best [5,6,7] Murray [62], Jorpes[47,48] and Jaques[45].

Mechanism of action:—Heparin inhibits the first phase of the clotting process by preventing the conversion of prothrombin to thrombin. However, adding a large amount of thromboplastin promptly results in clot formation.

Heparin may act by preventing the formation of thrombin by combining with thromboplastin so as to prevent it from activating prothrombin, or it may combine with prothrombin to form a complex which can be removed by excess of thromboplastin, as postulated by

Howell[38]. Heparin inhibits serum tryptase[76], and Ferguson[22] believes that serum tryptase participates in the activation of prothrombin. However, the concentration of heparin required to inhibit serum tryptase is considerably higher than that required to prevent clotting and so the anticoagulant role of heparin can hardly be ascribed to tryptase inhibition. The exact mechanism of the action of heparin is at present not well understood and must await fuller understanding of the reactions concerned in the conversion of prothrombin to thrombin.

Recently, Abrahams and Howarth[1] using a plethysmograph have shown that after therapeutic doses of intravenous heparin, there was a significant rise in the forearm blood flow and they opine that this rise in peripheral flow was brought about by a direct vasodilator action of heparin. This would indeed be a strong argument in favour of the use of heparin. Further reports are awaited on this subject. It is not known at present whether dicumarol has a similar action.

Heparin is inactive by mouth, and therefore, has to be given parenterally. When a single dose is injected intravenously, the clotting time rises swiftly to a peak, within about 10 minutes, and the anticoagulant action disappears within a few hours[43]. Jaques[44] has described an enzyme, heparinase, which probably accounts for the rapid disappearance of active heparin from the body.

Mode of administration:—Continuous intravenous infusion of heparin recommended by Murray and Best[63] has never gained popularity, because of the inconvenience in using a continuous drip and the danger of infusing large volumes of fluid in patients with cardiac failure. Jorpes[48] and other Swedish workers have used the intermittent intravenous technique successfully. Heparin is given in doses of 50 to 150 mg. every 4 to 6 hours during the day and the last dose at night, somewhat larger. None is given during the night. The total daily dose is about 350 to 400 mg. With this technique, it is not possible to maintain a steady and optimum anticoagulant effect. It is obvious that the clotting time fluctuates over a wide range, being maximum after each injection and minimum during the early hours of the morning.

Depot Heparin:—Attempts have been made to overcome the difficulty of giving repeated intravenous injections by using the intramuscular route. Loewe[54] has recently succeeded in prolonging the effect of a single dose considerably by deep subcutaneous deposition of 400 mg. of heparin in a special gelatin medium called the Pitkin menstruum. The effect appears within one to two hours and remains for 48 hours or longer. Loewe claims that injections of 400 mg. of heparin by Pitkin menstruum given on alternate days would maintain the coagulation time at its optimal level which is about three times the control value. This new preparation is said to be relatively painless. The work of Levinson[30] and De Takats[18], however, suggests that as a result of a single injection of this depot heparin, blood coagulation time is maintained within the optimum range for 24 to 36 hours only. They, therefore, recommend that blood coagulation time should be determined once a day and injections of heparin given at intervals of 24 to 36 hours.

DICUMAROL

Dicumarol, the second anticoagulant of great importance, was described, isolated and synthesized by Link[12, 13, 14, 52, 84]. University of Wisconsin. Dicumarol is readily synthesized and is therefore inexpensive.

Mechanism of action :—In vitro, dicumarol has no inhibitory action on blood clotting. Its anticoagulant action is due chiefly to its suppression of prothrombin formation in the liver. Whether it acts by competing with vit. K in the reactions concerned with the synthesis of prothrombin as suggested by Woolley[89] or by decreasing one of the proteins present in plasma or serum that accelerate the conversion of prothrombin to thrombin[68] is still a moot point.

The claim that dicumarol is toxic to the liver can be discounted in view of the experimental data[29], [57], which have not shown any morphological changes in the liver, either gross or microscopical. The available data suggest that in therapeutic doses dicumarol produces a specific biochemical lesion and not a diffuse damage to the liver.

Dicumarol is readily absorbed from the gastro-intestinal tract, and only a small portion may pass unchanged in the faeces. Nothing is known of its distribution and fate. Only traces of dicumarol can be detected spectroscopically in the blood of rabbits.[53] No dicumarol can be detected in the urine of dogs[67], although after nephrectomy [54] or kidney disease the effect of a single dose of dicumarol is greatly prolonged.

Dicumarol is slow in its action and the maximal effect of a single dose is attained after two or three days. This delay probably represents the time needed for the stores of prothrombin in the body to be exhausted. The sensitivity and duration of action of dicumarol varies greatly from patient to patient and the prothrombin activity does not return to normal level for a week to ten days after stopping the drug.

While heparin interferes with the reactions of coagulation, dicumarol affects the formation of one of its reactants. This difference is fundamental and accounts for the absolute dissimilarity between the pharmacological properties of heparin and dicumarol.

Mode of administration :—Dicumarol is administered orally. Barker[3] and others have established that there is little danger of hæmorrhage when prothrombin activity is above 10 per cent of normal. As thrombosis seldom occurs when prothrombin activity is less than 30 per cent of normal, the optimum therapeutic range of prothrombin activity is between 10 per cent to 30 per cent of normal. Ordinarily, 300 mg. is given as an initial dose and thereafter, the dose is adjusted according to the prothrombin activity determined each day. The average daily requirement is about 100 mg. a day.

As the effectiveness and safety of dicumarol administration depends entirely on reliable prothrombin determinations, it is not advisable to use dicumarol unless the facilities of a properly equipped chemical laboratory are available. Prothrombin activity is determined by various methods. The 'two-stage' method of Smith[86] and his co-workers, although it provides a more exact estimate of prothrombin concentration, is too intricate and cumbersome for general use. The one stage method of Quick [73] or Link-Shapiro modification is most extensively used. The relation between the prothrombin time and prothrombin concentration is not linear and therefore, a standard curve showing the prothrombin time for various prothrombin concentrations (obtained by diluting plasma with saline or prothrombin free plasma) should be prepared whenever a new batch of thromboplastin is used, and this curve should be used to determine the prothrombin concentration of the patient from the prothrombin time obtained for him.

As preparations of thromboplastin differ in potency [41], [16]. each new preparation has to be tested on several normal plasmas to determine the normal prothrombin time for every batch of thromboplastin. As thromboplastin deteriorates on storage, for determining the prothrombin time of a patient, 'control prothrombin time' has to be determined on a 'supposedly normal' person. It may be possible to get over this difficulty by using a stable thromboplastin. Shapiro[81] and his associates have described a new preparation 'Simplastin' which is thromboplastin of lung and brain tissue dried under high vacuum, which is ready for use after the addition of only distilled water. They claim that this thromboplastin is constant in its activity so that a normal range is fixed. It is stable within wide temperature ranges and does not deteriorate even after storage for many days.

The danger of bleeding is slight if the drug is not used in a condition in which it is contra-indicated. The administration of dicumarol is fraught with danger in the following conditions:

(1) Hæmorrhagic tendencies.
(2) Open wounds or ulcerations specially of the gastro-intestinal tract.
(3) Hepatic damage, because the synthesis of prothrombin may already be impaired.
(4) Kidney disease, because the duration of action is greatly prolonged.
(5) Severe hypertension, because of the danger of cerebro-vascular accident.

(6) Recent operations on the brain or spinal cord.

Penicillin introduced into the circulation accelerates coagulation[61] and gives rise to thrombus formation by inhibiting the acceleration of thrombin, probably, by way of the oxidising activity of its SH group. This fact must be borne in mind while giving anticoagulant therapy to patients receiving massive doses of penicillin.

CONTROL OF HÆMORRHAGE

Heparin is neutralised by protamin[71]. Bleeding from heparin can be promptly controlled by slow intravenous injections of protamine sulphate or toluidin blue, 1 to 3 mg. per kilogram of body weight. With depot heparin repeated injections are needed.

Bleeding from dicumarol can be effectively controlled by transfusions of fresh whole blood or fresh plasma. Large doses of vitamin K, 50 to 100 mg. given every 2 to 4 hours reduces the prothrombin activity to a safe level within 24 hours[17].

Vitamin K, is said to be superior as it has a more sustained effect[42], Miller[50] *et al*, are of the opinion that water soluble vitamin K has no antagonistic effect, and vitamin K, and to a lesser degree vitamin K oxide are very effective in decreasing the prothrombin time.

CHOICE OF DRUG

Heparin is the drug of choice, easy to control and quick in its action. However, it is very expensive, and therefore cannot be used as a routine. Dicumarol, being a synthetic preparation, is very cheap.

It is often desirable to start with heparin and dicumarol simultaneously. Heparin is discontinued as soon as a satisfactory level of prothrombin activity is achieved, which takes about 48 hours. Dicumarol is continued and optimum prothrombin activity maintained.

OTHER ANTICOAGULANTS

Gibson[27] has recommended the use of salicylates in cardiac infarction. A recent analysis by Levibond,[55] shows that massive daily doses of over 200 gr. are required for a satisfactory prolongation of the prothrombin time. With these high doses, symptoms of salicylism are prominent and reduction of doses causes unpredictable variation of prothrombin time. Personal variation was considerable, but no dangerous complications occurred. It may be recommended as an unpleasant but safe anticoagulant for domiciliary use.

Hirudin :—Hirudin[48] is present in the buccal glands of leeches. Its preparation is very expensive. Its action is unlike that of heparin and is supposed to inactivate thrombin as well as thrombokinase. *In vitro* it is 30 to 50 times weaker than heparin. It is, therefore, not possible to lengthen the clotting time to therapeutc requirements by the application of leeches.

NEWER ANTICOAGULANTS

3, 3[1]—*Carboxymethylenebis* (4—hydroxy-coumarin) ethyl ester. (tromexan, pelentan).

It is another coumarin derivative and its mode of action is similar to that of dicumarol [10, 11, 33]. It has approximately one-fifth the potency of dicumarol, has a faster absorption, and produces hypoprothrombinemia to therapeutic levels within 18 to 24 hours. The prothrombin level returns to normal in 48 to 60 hours. The administration of this drug has to be controlled by daily prothrombin time determinations similar to that of dicumarol.

Phenylindiom :—Its action is intermediate between heparin and dicumarol, but it resembles the latter more closely. It takes about 28 hours for the prothrombin level to reach 25 to 30 per cent of normal and takes about 36 to 48 hours to return to normal level after stopping the drug. Vit. K has no effect on the prolonged prothrombin time.

Paritol [83]:—This is a polysulfuric acid ester of polyanhydro-mannuronic acid. It produces a significant prolongation of clotting time. Its anticoagulant effect is 2 to 3 times longer than heparin, but untoward reactions are more common.

ANTICOAGULANTS IN THE TREATMENT OF MYOCARDIAL INFARCTION.

The ever present challenge of this disease is best brought home to the physician, when he realises that approximately 20 per cent of the members of his own profession in the United States of America, are stricken fatally with coronary thrombosis[19]. Exact statistical data are not available in India, but it appears that similar figures would be obtained.

In 1938 Best [82] and his co-workers used heparin in the management of experimental coronary thombosis.

They proved experimentally that dogs in whom the coronary artery was ligated and endocardium damaged by sodium resinoleate, mural thrombi were prevented by the previous administration of heparin. The rationale for the use of anticoagulants in myocardial infarction is based on the following principles :

1. To prevent the formation of intracardiac mural thrombi.
2. To prevent an extension of the thrombus from its point of origin, either proximally or distally.
3. To prevent the formation of venous thrombi in peripheral vessels, which are likely to cause pulmonary embolism.
4. To safeguard against thrombosis of the peripheral arteries.

As noted previously, the incidence of thrombo-embolic phenomena and resulting mortality is high in myocardial infarction. Various workers, [72, 69, 21, 56, 29, 28, 85, 54, 78], have reported that the incidence of thrombo-embolic phenomena and the mortality has been considerably reduced by the administration of anticoagulants. However, it is difficult to evaluate the effectiveness of anticoagulant therapy in a given patient with myocardial infarction, since we are unable to predict with certainty which patients will have a rapid series of thrombosis and embolic phenomena resulting in death, and which will have an uneventful recovery. As most of the series reported above have been rather small, no definite statistically significant conclusions could be drawn. To overcome this difficulty in the United States of America, a committee for the evaluation of anticoagulants in the treatment of coronary thrombosis was established by the American Heart Association and they have studied in detail a total of 1031 cases [90], [91], [92]. Of these 442 were given conservative treatment for coronary thrombosis and these served as a control group. The remaining 589 patients received the same treatment as above but were given in addition anticoagulants heparin and dicumarol. (Table 1.)

TABLE 1.—*Evaluation of Treatment of Coronary Thrombosis.*

	Control group.	Anticoagulant treated group.
Mortality	23.4%	16.0%
Thrombo-embolic complications	26.0%	10.9%
Number of thrombo-embolic complications per 100 cases	41.8	13.1
Secondary myocardial extension of infarcts	9.7%	3.2%
New infarcts	6.1%	1.9%
Pulmonary emboli	11.6%	4.8%
Cerebral emboli	4.9%	0.7%
Peripheral emboli	2.7%	0.5%

Thus one person in three who would be expected to die of myocardiac infarction will survive as a result of anticoagulant treatment. Similarly, more than one half of the anticipated thrombo-embolic complications could be prevented.

There were 15.3 episodes of bleeding per 100 cases in the group treated with anticoagulants as against 5.9 episodes in the control group. Of these 15.3 episodes, 2.7 occurred before the commencement of anticoagulants and 3.4 were believed to be due to causes other than anticoagulants, leaving 9.2 that could be attributed to anticoagulant therapy. Hæmaturia was the commonest manifestation and occurred in 7 episodes per 100 cases. It was microscopic in 5.3 episodes and gross in 1.7. Hæmoptysis was noted in 1.8 episodes per 100 cases as against 3.2 in the anticoagulant treated group. Deaths in the anticoagulant treated group which could be attributed to anticoagulant therapy were ½ to ¾ per cent, while 7.4 per cent of lives were saved as a result of anticoagulant treatment.

Extravasation of blood into the atheromatous plaque in coronary atherosclerosis, is thought at times to be a primary factor in acute closure of a coronary artery. Parker[68] *et al* are of opinion that the occurrence of an acute obstruction of a coronary artery secondary to sub-intimal hæmorrhagic lesions is rare and they did not find an increased incidence at autopsy, of such sub-intimal hæmorrhages in patients treated with anticoagulants, which they certainly would have, if such lesions were produced or aggravated by anticoagulants.

Anticoagulant treatment like other forms of medical treatment requires special skill for their use as these drugs are not without their hazards. However, their calculated risk is justified in return for the high dividends in terms of life saving and reduced disability. Anticoagulants should, therefore, be administered to every patient suffering from acute coronary thrombosis, unless definite contraindications for its use exist.

ANTI-COAGULANTS IN CONGESTIVE CARDIAC FAILURE

Anderson *et al*[2] in a series of 297 patients of congestive cardiac failure, 147 of whom were treated with anti-coagulants, report a mortality of 13.3 per cent in the control group as against 7.5 per cent in the treated group. The number of deaths from definite or proved thrombo-embolism was zero in the treated as against 9 in the control group. Similarly, Wishart and Chapman[87] in a series of 61 patients of definite congestive heart failure who were given dicumarol, reported an incidence of thrombo-embolic phenomena in 6.5 per cent of cases, as against 22 per cent reported by other workers in cases where anticoagulants were not administered. Similarly, in this series, no deaths could be attributed with certainty to massive pulmonary embolism, except one which might conceivable have been due to such an accident.

From these data it appears that anticoagulants give a high degree of protection to cardiac patients in congestive failure from thrombo-embolic complications.

LONGTERM ANTICOAGULANT THERAPY

Continuous anticoagulant therapy must be considered in :—

1. Recurrent emboli in rheumatic heart disease or myocardial infarction.
2. Recurrent attacks of coronary thrombosis and myocardial infarction.

Rice[74] and his associates have described a 48 year old physician who experienced numerous episodes of coronary insufficiency with myocardial infarction complicated by frequent pulmonary infarctions. Continuous use of dicumarol for about 20 months prevented further episodes of coronary thrombosis or pulmonary infarctions. When dicumarol was discontinued after 20 months, a further episode, three months after its discontinuance, occurred. Continuous administration of dicumarol since has prevented further attacks.

Similarly, Wright [24], [91]. *et al* report a series of 22 patients of rheumatic heart disease or myocardial infarction who were getting repeated thrombo-embolic complications. They were put on continuous dicumarol therapy from a few months to over 19 months. There have been no further embolic phenomena since the institution of anticoagulant therapy in those who were maintained at optimum prothrombin levels.

Nichols [65], [66] *et al* have given continuous dicumarol therapy to 78 patients following an attack of acute coronary thrombosis and for myocardial infarction. The results are encouraging but no statistically significant conclusions could be drawn as the series is a small one.

It is, threfore, desirable to institute long term anticoagulant therapy in patients getting recurrent emboli in rheumatic heart disease or myocardial infarction, and in repeated attacks of coronary thrombosis and myocardial infarction.

SUMMARY

Statistical data is presented which shows an increased incidence of thrombo-embolic complications in heart diseases.

Factors leading to thrombus formation are discussed and the clinical features of thrombo-embolic phenomena are briefly enumerated.

At present the two anticoagulants in common use are heparin and dicumarol. Heparin inhibits the clotting process by preventing the conversion of prothrombin to thrombin and thus prolonging the coagulation time.

It is quick in its action but has to be given parenterally. About 350 to 400 mg. of heparin have to be administered per day to maintain the coagulation time at its optimum therapeutic level, which is about three times the control value.

Dicumarol acts by suppression of prothrombin formation in the liver. It is given by mouth and takes about 2 to 3 days for the maximal effect to be produced. Ordinarily 300 mg. are given as an initial dose and the subsequent doses adjusted to keep the prothrombin activity between 10 per cent to 30 per cent of normal. The average daily requirement is about 100 mg. It is desirable to start with heparin and dicumarol simultaneously and to discontinue heparin as soon as satisfactory prothrombin activity is achieved. Contra-indications for the use of dicumarol are given. It should not be used unless the facilities of a properly equipped chemical laboratory are available.

Recent statistical data are presented which shows that as a result of anti-coagulant therapy in myocardial infarction, one person in three who would be expected to die will survive. Similarly, the incidence of thrombo-embolic complications is reduced from 26 per cent to 10.9 per cent.

Statistical data suggest that anti-coagulants are useful in giving a high degree of protection from thrombo-embolic complications to cardiac patients in congestive failure.

Long term anticoagulant therapy appears to be beneficial in recurrent emboli in rheumatic heart disease or myocardial infarction; and in recurrent attacks of coronary thrombosis and myocardial infarction.

REFERENCES

1. Abrahams, D. G., and Howarth: Proceedings of British Cardiac Society. A Peripheral Action of Heparin, Brit. Heart. J. **12**: 429, 1950.
2. Anderson, G. M., Hull, E.: The Effect of Dicumarol Upon the Mortality and Incidence of Thrombo-embolic Complications in Congestive Heart Failure, Am. Heart J. **39**: 697-702, 1950.
3. Barker, N. E., Cromer, H. W., Hurn, M., and Waugh, J. M.: Use of Dicumarol in Prevention of Post Operative Thrombosis and Embolism with Special Reference to Dosage and Safe Administration, Surgery **17**: 207-217, 1945.
4. Bauer, G.: Thrombosis: Early Diagnosis and Abortive Treatment with Heparin, Lancet **1**: 447-454, 1946.
5. Best, C. H., Charles, A., and Cowan, C.: The Administration of Heparin, Am. J. Physiol **19**: 272, 1936.
6. Best, C. H., Cowan, C., and McLean, D. L.: Heparin and Formation of White Thrombi, J. Physiol. **92**: 20-31, 1938.
7. Best, C. H.: Heparin and Thrombosis. Harvey Lectures **36**: 66-90, 1941.
8. Blaustein, A. U., Croce, J. J., Alberian, M., and Richey, N.: Preliminary report on the Clinical Use of a New Anticoagulant, Phenylindandione, Circulation **1**: 1195-1204, 1950.
9. Brinkhous, K. M., Amith, H. P., Warner, E. D., and Seegers, W. H.: Inhibition of Blood Clotting: Unidentified Substance which Acts in Conjunction With Heparin to Prevent Conversion of Prothrombin into Thrombin, Am. J. Physiol. **125**: 683-687, 1939.
10. Burke, G. E., and Wright, I. S.: Tromexan-3, 31-Carboxymethyl-enebis (4-Hydroxycoumarin) Ethy; Ester. Experimental and Clinical Properties, Circulation. **3**: 164-170, 1951.
11. Burt, C. C., Wright, H. P., and Kubik, M.: Clinical Tests of a New Coumarin Substance, B. M. J. **2**: 1250-1254, 1949.
12. Campbell, H. A., Roberts, W. L., Smith, W. K., and Link, K. P.: Studies on the Hemorrhagic Sweet Clover Disease. 1. The Preparation of Hemorrhagic Concentrates, J. Biol. Chem. **136**: 47, 1940.
13. Campbell, H. A., Roberts, W. L., Smith, W. K., and Link, K. P.: Studies on the Hemorrhagic Sweet Clover Disease. II. The Bio-Essay of Hemorrhagic Concentrates by Following the Prothrombin Level in the Plasma of Rabbit Blood, J. Biol. Chem. **138**: 1, 1941.
14. Campbell, H. A., and Link, K. P.: Studies on the Hemorrhagic Sweet Clover Disease. IV. Isolation and Crystallization of the Hemorrhagic Agent, J. Biol. Chem. **138**: 21, 1941.

15. Charles, A. F., and Scott, D. A.: Studies on Heparin. IV Observations on the Chemistry of Heparin, Biochem, J. **30**: 927, 1936.
16. Conley, C. L., Morse, W. I. H, and Stewart, E. E.: Thromboplastic Factors. in Estimation of Prothrombin Concentration, Am. J. M. Sc. **215**: 158-169, 1948.
17. Cromer, H. E. Jr., and Barker, N. W.: Effect of Large Doses of Menadione Bisulfite (Synthetic Vit. K.) on Excessive Hypoprothrombinemia Induced by Dicumarol, Proc. Staff Meet., Mayo Clin. **19**: 217-233, 1944.
18. De Takats,: The Subcutaneous Use of Heparin, Circulation. **2**: 837-844, 1950. 1950.
19. Editorial: Deaths of Physicians in 1944, J. A. M. A. **127**: 90-91, 1945.
20. Emmel, V. M., and Dam, H.: Absence of Liver Damage in Chicks Hypoprothrombinemic due to Vit. K. Deficiency or Ingestion of 3, 31- Methylenebis (4-Hydroxy-coumarin). Proc. Soc. Exper. Biol. & Med. **56**: 11-14, 1944.
21. Falk, O. P. J.: Treatment of Coronary Artery Disease, J. A. M. A. **134**: 491-496, 1947.
22. Ferguson, J. H.: Heparin and Plasma Albumin in Relation to Thromboplastic Action of Trypsin, Cephalin and Brain Extracts, Proc. Soc. Exper. Biol and Med. **42**: 33-37, 1939.
23. Flynn, J. F.: Blood Clotting and Allied Problems: Transactions of the First Conference, February 16-17, 1948, New York, pp. 179, New York, Josiah Macy, Jr., Foundation, 1948.
24. Foley, W. T., and Wright, T. S.: Longterm Anticoagulant Therapy for Cardiovasular Diseases, Am. J. M. Sc. **217**: 136-142, 1949.
25. Fuld, E, & Spiro, K.: Der Einfluss Einiger Gerinnungshemmender Agentian auf das Vogelplasma. Beitr. Z. Chem. Physiol. U. Path. **5**: 171-190, 1904.
26. Garvin, C. F.: Mural Thrombi in Heart, Am. Heart J. **21**: 713-720, 1941.
27. Gibson, P.: Salicylic Acid for Coronary Thrombosis, Lancet. **1**: 965, 1948.
28. Gilchrist, Rae, and Tullock, J.: Proc. Brit. Cardiac Soc.: Discussion on the Use of Anticoagulants, Brit. Heart J. **12**: 425-427, 1950.
29. Glueck, H. I., Strauss, V., Pearson, J. S., and McGuire, J.: Combined Heparin-Dicumarol Therapy of Myocardial Infarction: Clinical and Pathological Study, Am. Heart J. **35**: 269-281, 1948.
30. Glueck, H. I., Podore, G. J., and Levinson, J. E.: Efficiency of Heparin in Retarding Media on the Maintenance of a Decreased Coagubility of the Blood, Circulation. **2**: 530-535, 1950.
31. Greenstein, J.: Thrombosis and Pulmonary Embolism, South African M. J. **19**: 350 and 377, 1945.
32. Hampton, A. O., and Castleman, B.: Correlation of Postmortem Chest Telerocutgenograms with Autopsy Findings: With Special Reference to Pulmonary Embolism and Infarction, Am. J. Roentgenol. **43**: 305-306, 1940.
33. Hausner, E. P., Shafer, C. L., Corson, M., Johnson, O., Trujillo, T., and Langham, E W.: Clinical Evaluation of Dicumarinyl Derivatives with a Metabolic Study of Radioactively Labelled Anticoagulants in Animals, Circulation **3**: 171-181, 1951.
34. Hellerstein, H. K., and Martin, J. W.: Incidence of Thrombo-Embolic Lesions Accompanying Myocardial Infarction, Am. Heart J. **33**: 443-452, 1947.
35. Hines, L., and Hunt, J.: Pulmonary Infarction in Heart Disease, Ann. Int. Med. **15**: 644-647, 1941.
36. Homans, J.: Venous Thrombosis in the Lower Limbs: Its Relation to Pulmonary Embolism, Am. J. Surg. **38**: 316-326, 1937.

37. Howell, W. H.: Coagulation of Blood, Harvey Lectures. **12**: 272-323, 1918.

38. Howell, W. H. and Holt, E.: Two New Factors in Blood Coagulation-Heparin and Pro-Antithrombin, Am. J. Physiol. **47**: 328-341, 1918.

39. Howell, W. H.; Purification of Heparin and Its Chemical and Physiological Reactions, Bull Johns Hopkings Hosp. **42**: 199-206, 1928.

40. Hunter, W. C., Sneeden, V. D., Robertson, T. D., and Snyder, G. A. C.: Thrombosis of the Deep Veins of the Legs. Arch. Int. Med. **68**: 1-17, 1941.

41. Hurn, M., Barker, N. W., and Magath, T. B.: Prothrombin Time Determinations Following Administration of Dicumarol, With Special Reference to Variability of Thromboplastin, Proc. Staff Meet., Mayo Clin. **19**: 507-512, 1944.

42. James, D. F., Bennett, I. L., Jr., Scheinberg, P., and Butler, J. J.: Clinical Studies on Dicumarol Hypoprothrombinemia and Vitamin K. Preparations. 1. Superiority of Vitamin K Oxide over Menadione Sodium Bisulfite U.S. P. and Synkavite in Reversing Dicumarol Hypoprothrombinemia, Arch. Int. Med. **83**: 632-652, 1949.

43. Jaques, L. B.: Effect of Intravenous Injections of Heparin in Dog, Am. J. Physiol. **125**: 98-107, 1939.

44. Jaques, L. B.: Heparinase, J. Biol. Chem., **133**: 445-451, 1940.

45. Jaques, L. B., and Waters, E. T.: Isolation of Crystalline Heparin from Blood of Dogs in Anaphylactic Shock, Am. J. Physiol. **129**: 389, 1940.

46. Jaques, L. B., Gordon, E., and Lepp., E.: A New Prothrombopenic Drug, Phenylindanedione, Canad. M. A. J. **62**: 465-470, 1950.

47. Jorpes, E.: Heparin: Its Chemical Nature and Properties, Acta Med. Scandinav. **88**: 427-433, 1936.

48. Jorpes, J. E.: Heparin in the Treatment of Thrombosis: An Account of its Chemistry, Physiology and Application in Medicine, pp. 206 London, Oxford University Press, 1946.

49. Kinsey, D., and White, P.: Fever in Congestive Failure, Arch. Int. Med. **65**: 163-170, 1940.

50. Kirby, C. K.: Venous Thrombosis and Pulmonary Embolism, Surg. Clin. N. Am. **26**: 1389, 1946.

51. Levine, S. A., and Brown, C. S.: Coronary Thrombosis: Its Various Clinical Features, Medicine, **8**: 245-418, 1929.

52. Link, K. P.: Anticoagulant from Spoiled Sweet Clover Hay. Harvey Lectures. **39**: 162-216, 1944.

53. Link, K. P., Overman, R. S., Sullivan, W. R., Huebner, C. F., and Scheel, L. D.: Studies on Hemorrbagic Sweet Clover Disease. XI. Hypoprothrombinemia in Rat Induced by Salicylic Acid, J. Biol. Chem. **147**: 463-474, 1943.

54. Loewe, L., Eiber, H. B.: Anticoagulant Therapy with Heparin-Pitkin Menstruum in the Management of Coronary Artery Thrombosis and Its Complications, Am. Heart J. **37**: 701, 1949.

55. Lovibond, J. L.: Proc. Brit. Cardiac Soc., Salicylate as an Anticoagulant, Brit. Heart J. **12**: 429, 1950.

56. McCall,, M.: Dicumarol Therapy in Acute Coronary Occlusion with Myocardial Infarction, Am. J. M. Sc., **215**; 612-616, 1948.

57. McCarter, J. C., Bingham, J. B., and Meyer, O. O.: Studies on Hemorrhagic Agent 3, 31-Methylenebis (4-Hydroxycoumarin). IV. Pathologic Findings. After Administration of Dicumarol, Am. J. Path. **20**: 651-659, 1944.

58. McLean, J.: Thromboplastic Action of Cephalin, Am. J. Physiol. **41**: 250-257, 1916.

59. Miller, A. B., Harvey, W. P., and Finch, C. A.: Antagonism of Dicumarol by Vitamin K. Preparations, N. E. J. Med. **242**: 211-215, 1950.

60. Morawitz, P.: Zur Kenntnis der Vorstufen des Fibrinferments, Beitr. Z. Chem. Phys. U. Path. **4**: 381-420, 1904.

61. Mosonyi, L., Palos, L. A., and Komaromy, J.: Penicillin and Blood Coagulation, Acta Med. Scandinav. **135**: 458-464, 1949.

62. Murray, D. W. G., Jaques, L. B., Perett, T. S. and Best, C. H.: Heparin and Thrombosis of Veins Following Injury, Surgery **2**: 163-187, 1937.

63. Murray, D. W. G, and Best, C. H.: Use of Heparin in Thrombosis, Ann Surg, **108**: 163-177, 1938.

64. Nay, R. M., and Barnes, A. R.: Incidence of Embolic or Thrombotic Process During the Immediate Convalescence from Acute Myocardial Infarction, Am. Heart J. **30**: 65-76, 1945.

65. Nichol, E. S., Borg, J. F.: Long-term Dicumarol Therapy to Prevent Recurrent Coronary Artery Thrombosis, Circulation **1**: 1097-1104. 1950.

66. Nichol, E. S., Fassett, D. W.: An Attempt to Forestall Acute Coronary Thrombosis, South M. J. **40**: 631-637, 1947.

67. Overmann, R. S., Field, J. B., Bauman,, C. A., and Link, K. P.: Studies on Hemorrhagic Sweet Clover Disease. VII. Effect of 3, 31-Methylenebis (4-Hydroxycoumarin) on Prothrombin Time of Plasma of Various Animals, J. Biol. Chem. **142**: 941-955, 1942.

68. Own, C. A., and Bollman, J.L.: Prothrombin Conversion Factor of Dicumarol Plasma, Proc. Soc. Exper. Bio.. and Med. **67**: 231-234, 1948.

69. Parker, R. L., and Barker, N. W.: The Use of Anticoagulants in the Management of Acute Myocardial Infarction, Proc. Staff Meet., Mayo Clin. **22**: 185-192, 1947.

70. Parker, R. L., Barker, N. W.: The Effects of Anticoagulants on the Incidence of Thrombo-Embolic Complications in Acute Myocardial Infarction, Proc. Staff Meet., Mayo Clin. **23**: 367-378, 1948.

71. Parkin, T. W., and Kvale, W. F.: Neutralization of Heparin with Protamin (Salmine), J. Lab. and Clin. Med. **32**: 1396, 1947.

72. Peters, H. R, Guyther, J. R., and Brambel, C. E.: Dicumarol in Acute Coronary Thrombosis, J. A. M. A. **130**: 398-403, 1946.

73. Quick, A. J.: On Quantitative Estimation of Prothrombin, Am. J, Clin. Path. **15**: 560-566, 1945.

74. Rice, R. L, Ackerman, J. S, and Saichek, R.: Long Term Dicumarol Therapy, Ann. Int. Med. **32**: 735-744, 1950.

75. Richards, R. K, and Steggerda, F. R.: Dicumarol (3, 31-Methylenebis (4-Hydroxycoumarin) in Rats with Impaired Liver or Kidney Function, Proc. Soc. Exper. Biol. and Med. **52**: 358-360, 1943.

76. Rocha e Silva M., and Andrade, S. O.: Antagonism Between Heparin and Plasma Trypsin, Science **102**: 670, 1945.

77. Sagall, E. L., Bornstein, J., and Wolff, L.: Clinical Syndrome in Patients with Pulmonary Embolism. Arch. Int. Med. **76**; 234-238, 1945.

78. Schilling, F. J.: Anticoagulants in Myocardial Infarction, J. A. M. A. **143**: 785-789, 1950.

79. Seegers, W. H.: Blood Coagulation and the Practical Significance of Recent Advances in Knowledge of Prothrombin and Ac-Globulin, Circulation **1**: 2-9, 1950.

80 Seegers, W. H., and Ware, A. G.: Protein Equilibrium Reactions in Blood Clotting Mechanism. In Blood Clotting and Allied Problems, 13 Pp. 64-84.

81. Shapiro, S., Weiner, M., Luddecke, H. F., Kroc, R. L., and White, E. J.: A Simply Prepared, Standardised, and Relatively Stable Thromboplastin Extract for Estimation of Prothrombin Time, Am. Heart J. **40**: 766-770, 1950.

82. Solanat, D. Y., Nassim, R., and Best, C. H.: Production and Prevention of Cardiac Mural Thrombosis in Dogs, Lancet **2**: 592-595, 1939.

83. Sorenson, C. W., and Wright, I. S.: A Synthetic Anticoagulant: A Polysulfuric Acid Ester of Polyanhydromannuronic Acid (Paritol), Circulation **2**: 659-667, 1950.

84. Stahman, M. A., Huebner, C. F., and Link, K. P.: Studies on the Hemorrhagic Sweet Clover Disease. V. Identification and Synthesis of the Hemorrhagic Agent, J. Biol. Chem. **138**: 513-527, 1941.

85. Tulloch, J. A., and Gilchrist, A. Rae: Anticoagulants in the Treatment of Coronary Thrombosis, B. M. J. **2**: 965-970, 1950.

86. Warner, E. D., Brinkhous, K. M., and Smith H. P.: Quantitative Study on Blood Clotting: Prothrombin Fluctuations Under Experimental Conditions, Am. J. Physiol. **144**: 667-675, 1936.

87. Wishart, J. H. and Chapman, C. B.: Dicumarol Therapy in Congestive Heart Failure, N. E. J. Med. **239**: 701-704, 1948.

88. Wolff, L., and White, P.D.: Acute Coronary Occlusion, 23 Autopsied Cases, Boston Med. and Surg. J. **195**: 13-25, 1926.

89. Wolley, D. W.: Recent Advances in Study of Biological Competition Between Structurally Related Compounds, Physiol. Rev. **27**: 308-333, 1947.

90. Wright, I. S., Marple, C. D., Beck, D. F.: Report of the Committee for the Evaluation of Anticoagulants in the Treatment of Coronary Thrombosis with Myocardial Infarction, Am. Heart J. **36**: 801, 1948.

91. Wright, I. S.: The Use of Anticoagulants in the Treatment of the Diseases of the Heart and Blood Vessels, Ann. Int. Med. **30**: 80-91 1949.

92 Wright, I S.: Clinical Progress: The Modern Treatment of Coronary Thrombosis with Myocardial Infarction, Circulation **2**: 929-936, 1950.

MISCELLANEOUS

CLINICAL RESEARCH IN INDIA

J. C. Patel *

As a physician, my first duty is to cure the ills of human beings. That is one of the Hippocratic Oaths. In order to do it successfully, I must follow Hippocrates, to observe the signs and symptoms of the illnesses and to advance clinical medicine. The advance can only be done by clinical research, and by observation of human beings. In the past, research in clinical problems, as opposed to work in the laboratory, had been done by great people like Lister, McKenzie, Addison, Hunter, Osler and a host of others. In the course of their routine work, they did valuable and accurate observations on their patients and it was by such work that they advanced clinical medicine. The sciences of chemistry and physics advanced rapidly during the last century and had their impact on medicine. The laboratory came into existence to help clinical medicine, and at one stage even more reliance was placed on laboratory findings than on clinical observations. At this stage, even though clinical research was important, it could not advance without the help of a laboratory. Sir Thomas Lewis combined clinical research with laboratory methods and produced a monumental amount of clinical work.

In the allied sciences like physiology and pharmacology, a large number of problems have been tackled to advance medical science, but in its application, research has to be carried out finally in human beings. An example can be given of antibiotics. In the course of the last six years, more than a hundred antibiotics have been discovered which are useful against a variety of organisms, both in a test tube and in animals in the laboratory. However, only about four or five of them have been applied successfully in clinical medicine, because some of them, even though very highly efficient in experimental diseases, are too toxic to be of any clinical use to man.

The final test of all research carried out in the laboratory—whether it is of a chemical, physical, physiological or pharmacological nature—is its applicability to human beings in the wards and that is where the physicians come in.

Clinical research in this country is neglected because there is not the atmosphere for it. There are not enough personnel, technical help and laboratory facilities. Due to a shortage of doctors in our country, most medical people are overworked with their routine clinical job, be it general practice or work in a teaching or a non-teaching hospital.

---

* Based on a lecture delivered before students of the Medical College, Amritsar, on 2nd April, 1951.

The traditional background also hinders it. Amongst the Indians; as amongst anybody else, too much importance is attached to the amount of money one acquires, and that applies to the medical profession. In a hospital, a physician or a surgeon is considered a better doctor if he has amassed a larger fortune than his fellow workers. That being so at the moment, the aim of the students, residents, civil servants (doctors) and honorary medical officers is to make money as much and as quickly as possible. However, this will change in the course of time because we do not lack in intelligence; but the progress is slow. We go to England or America for foreign qualifications or for a refresher trip, if we can afford it or if we are sent there. Why do we have to go there? Why don't I want to come to Amritsar or you to Bombay or Madras? *Why do we look up to these people and feel that we will learn something* more from this trip, apart from a pleasant holiday? Because one learns something new. By constant observations in medical sciences they are always advancing. It is to learn something new that we want to go there. A reputation of a medical school, in the long run, depends not on those people who have staffed it and have made large fortunes but on the amount of research work produced by that school. Large fortunes may be necessary to build a medical school but the beautifully equipped laboratory building is not all. In Guy's hospital, there were a large number of doctors who had a big practice, but we do not remember them as much as we remember Thomas Addison who had no material fortune to leave behind him.

We have a large amount of clinical material in our country particularly in tropical diseases. We should not depend on a German or a Frenchman for discovering the treatment of diseases common in our country. Recently, the American Army sent a unit to Malaya to test chloramphenicol in scrub typhus fever as they did not have enough clinical material of this disease in their own country. They had tested this drug in laboratory animals for which they had excellent facilities. We have clinical material but we do not bother to make scientific observation as a German would do.

It is the usual complaint of all the pharmaceutical houses trading in India that they cannot get any work of a nature of clinical trials carried out successfully in this country. It is because we are engaged and pay more attention to making money, whether with success or otherwise, is hardly of importance. It is certainly true that there is very little co-operation from other colleagues if one of us becomes enthusiastic. There is quite often lack of facilities in an institution because of the poverty of our country. It is also due, may be, to the ignorance of our people who form the clinical material for research. They will hardly carry out our instructions. They will not have continuous faith in one doctor or institution for a long time, or when they leave the hospital they will hardly ever return. In short, there is no follow up of a patient, which is an important matter in clinical research.

Another hindrance in clinical research is lack of beds and personnel. I have already mentioned that we have a shortage of doctors, but that can be minimised in medical research by employing trained technicians. In England and America these days, no qualified doctor, biochemist, physiologist or pharmacologist spends time on a routine work of research. It is handed over to a new class of people which is coming up, called technicians. It is a new occupation recently found for young boys and girls after their matriculation, just as we have clerks, typists, ticket-collectors,—they have technicians to help them in research work. There is a technician's course or a diploma given by various institutions or universities, and they make a career in a hospital or a laboratory. Girls make ideal technicians. They are good at a routine job and they can take it up for a few years before they embark on their usual natural profession of marriage. This class of technicians should be developed and encouraged in our country and it is we, who, as physicians, should help them to come up for the ultimate benefit of research in our country. A medical graduate would hardly be interested in a job of this kind in research which we are wanting him to do at this stage, but technicians would suit better. Such a graduate can do better, guiding the project.

Another disadvantage in our country is lack of facilities for an autopsy, and this could be remedied by an increase in the standard of education or by legislation.

Granting that all these facilities are available, there will always remain some hindrance from medical colleagues because of personal jealousy or prejudice, till all of them are full time workers or are interested in research. But in spite of all these difficulties we must advance and advance can only be done by willingness to do research work or by recognising the necessity for it. At this stage, in the whole of Asia, barring Japan, research and for that matter, clinical research is negligible. In political fields, Eastern nations are looking to India for leadership. The Indian Government is giving scholarships, called cultural scholarships, to the students of neighbouring countries to come and study in India. If there is an advance of clinical medicine in our country, all the Asian countries would come to India and would look up to this country for further studies. At present, we are hardly more advanced than our neighbours in Asia. Why should they come to us if we are no better? Let me hope that some of you, young, intelligent students will come forward and take up research to advance your personal prestige, that of your school and of your country as a whole.

CURRENT MEDICAL LITERATURE

MEDICINE

TREATMENT OF ALLERGIC DISEASE OF THE BRONCHI, Feingold, B. F.: J.A.M.A., **146**: 319-323, 1951. 6 References.

In the pathology of allergic diseases two types of tissue changes are observed: (1) the reversible and (2) the irreversible. The reversible tissue changes are produced by such antigens as pollens, epidermals, foods, serums and drugs and are characterised by edema, smooth muscle spasm and stimulation of glands. Edema of the peri-bronchial tissues produces rigidity of the bronchial tree thereby interfering with the normal expansile and contractile movements of these structures, while swelling of the mucosa encroaches on the lumens, which are also narrowed by smooth muscle spasm. These factors combined with the increased production of mucus resulting from stimulation of glands, create varying degrees of obstruction, which is the basic disturbance in bronchial allergic disease.

The first step towards definitive control of this disease is to determine the specific factors concerned: a thorough, complete and accurate history of the initial onset of any signs or symptoms of an allergic nature; the relation of the ailment to all possible environmental influences should be elicited; seasonal variation should be determined: influence of various food items accurately estimated and complemented with skin testing. The relief of edema and bronchospasm is obtained by sympathomimetic drugs, epinephrine, ephedrine and phenylpropanolamine (propadrine) which have a vasco-constrictor action in addition to their ability to relax the bronchospasm. Those drugs having a strong bronchodilator effect but no vasoconstrictor action do not influence the edema of allergic bronchial disease, but on the contrary predispose one to an aggravation of edema with its resulting influence upon the symptoms. Epinephrine is used in the acute asthmatic episode in the dosage of 0.3 cc. to 0.5 cc. subcutaneously; it can be repeated in rapidly successive doses without loss of effectiveness. Ephedrine hydrochloride or sulphate is employed to prevent the occurrence of acute episodes and to treat mild attacks of allergic bronchial disease. It is administered by mouth in doses of ⅛ gr. to children 1 year of age and under and in doses of ¼ gr. to older children. The drug should not be repeated too rapidly, as the effects diminish with each successive dose. In order to counteract unpleasant side effects of ephedrine, the drug should be combined with small doses, ⅛ gr. to ¼ gr. of phenobarbital. When ephedrine is not tolerated, propadrine may be substituted. The use of antihistaminics in allergic bronchial disease have been disappointing. Of the xanthine group of drugs, theophylline and aminophylline have enjoyed popularity in the treatment of this disease. Theophylline is commonly combined with ephedrine and phenobarbital as an anti-asthmatic for the mild attack. Aminophylline is administered orally in doses of 1½gr. or by suppository. It can also be given intravenously for the acutely asthmatic patients, especially when they are refractory to epinephrine. For the relief of mucus, expectorants are indicated. Water is the best of all expectorants. In the absence of an adequate fluid intake none of the medicinal expectorants are effective. At least 1,000 cc. of fluids should be administered per day. Of the various expectorant drugs available, a saturated solution of potassium iodide is the most effective. This can be administered in doses of 5 to 10gr. three times daily, depending on the age of the child. The *opiates and sedative cough mixtures are* contraindicated.

The irreversible, or fixed, tissue changes, which are induced by such antigens as bacteria, bacterial products, serums and drugs, are identified with death of cells and vascular damage. In the lungs such tissue alterations affect the respiratory portion of these organs, such as the parenchyma, the alveolar ducts and the terminal bronchioles. A history of either a bronchial asthma or of respiratory difficulty of a lesser degree with rhonchi, coarse rales and wheezes in the lungs, accompanied with an upper respiratory tract infection has been responsible for such terms as "asthmatic bronchitis" "allergic bronchitis," or "acterial asthma." The implication in each instance is that bacteria or bacterial products are the causative agents for the allergic state. The recognition of the role of infection is important in the management of allergic disease of the bronchi. For control of the acute symptoms in this syndrome, therapy in the form of the sulphonamides or of the antibiotics is directed against the infection. As the infection improves, the symptoms of allergic disease also improve. The complications of allergic bronchial disease are dehydration with consequent bronchial plugging, status asthmaticus, restlessness, cyanosis and fever. For dehydration and bronchial plugging, the most valuable measures are an adequate fluid intake and saturated solution of potassium iodide. The fluids may have to be administered intravenously (5 per cent glucose). Status asthmaticus usually results from dehydration. In most instances immediate response will be observed following the intravenous administration of 5 per cent glucose and epinephrine subcutaneously. For restlessness, phenobarbital in small doses is indicated. When cyanosis occurs, it is usually due to either atelectasis or infection or both. The same basic principles are applicable, adequate hydration, expectorants and specific therapy for infection. For cyanosis, oxygen therapy is indicated. High fever in allergic bronchial disease indicates the presence of infection as a precipitating agent, while sudden high temperature of 104 to 106°F suggests the complication of allergic broncho-pneumonia.

ERIC COELHO.

TREATMENT OF AMEBIASIS WITH BACITRACIN AND OTHER ANTIBIOTICS, Most H., Miller J. W. & Grossman, E. J.: Amer. J. Trop Med. **30**: 491-497 1950. (Trop. Dis. Bull. **47**: 1200 1950.)

Fifty-one cases of *E. histolytica* were treated with oral tablets of bacitracin. The daily dose varied from 40,000 to 120,000 units continuing over a perid of 5-20. days. 66 per cent of these were free from amœba. Repetition of treatment cured 33 per cent of the failures. Continuation of bacitracin treatment beyond a period of 10 days or an increase in the daily dosage beyond 80,000 units did not significantly increase the probability of cure beyond 66 per cent. Toxic effects were in the form of distension and diarrhœa. The drug is little absorbed from the intestine and there was hardly any concentration in the blood. The authors conclude that bacitracin is effective in terminating acute attacks of amœbic dysentery and ensures cure in two-thirds of cases of amœbiasis. Its action may be due to the disappearance of clostridia and enterococci from stools. Aureomycin seemed to act in a similar way.

J. C. PATEL.

ORTHOSTATIC ALBUMINURIA. A TIME-SAVING METHOD OF DIAGNOSIS, Watson, A: Lancet, **1**: 1196-1197, 1951.

The author describes a very simple test to detect orthostatic albuminuria, without the patient having to sleep overnight and then collecting the urine. It was a chance observation by the medical orderly of the author, who noticed that there was a higher proportion of patients with albuminuria (the great majority of them proving to be of orthostatic origin) on the days when they were not kept waiting at all before having the urine tested. The author adopted the following routine. When a patient was found to have albuminuria he was told to empty his bladder completely and was given half a pint of water to drink. He was then told to sit quite still in the waiting room until called. Further urine tests were made after 15, 30, 45 and 60 minutes after resting. 62 patients of albuminuria were thus tested. None excreted albumin in after 15 minutes' rest. A short period of rest after the bladder has been emptied is sufficient to produce an albumin-free urine in a youth who has orthostatic albuminuria.

D. D. VORA.

PNEUMOCOCCAL MENINGITIS, A REVIEW OF FORTY CASES, Simpson, W. H. and Holley, H. L.: Amer. Pract. 2: 486-490, 1951. 1 table 18 references.

The authors reviewed the records of patients with a diagnosis of pneumococcal meningitis admitted to the Jefferson-Hillman Hospital during the eight-year period from June 30, 1942 to June 30, 1950. Forty patients were selected, the diagnosis being made on the basis of either a positive culture of pneumococci from the cerebrospinal fluid or by post-mortem examination. The analysis showed that there were 21 females and 19 males. The disease was more common in adults; 25 cases occurring in patients over 15 years of age, whereas only 15 cases occurred in infants and children. The presenting symptoms were headache, vomiting and fever, and the classical signs of meningeal irritation were present consistently in adult patients. In infants, the meningeal signs were strikingly absent, whereas clinical findings of convulsions, vomiting, unexplained fever and a bulging fontanelle were common.

The two drugs used consistently, either concomitantly or separately, were sulfadiazine and penicillin. All cases receiving sulfadiazine, received daily doses, usually as repeated intravenous injections in addition to oral doses in excess of 1 Gm. every 4 hours. In most cases the sulfa drug was maintained for 5 to 6 days after the fever had subsided or until death supervened. Penicillin was administered intramuscularly in all but 9 cases, in the dosage of 50,00 units 3 hourly. The authors administered penicillin intrathecally in 25 cases, the dose ranging from 10,000 to 20,000 units per injection, one case receiving 50,000 units. There were 51 recoveries and 10 deaths which is the same as that for the entire series. Recently, toxic reactions, including arachnoiditis, myelitis, paraplegia, cauda equina damage, pain and weakness in the upper limbs and convulsions, have been attributed to this form of intrathecal therapy. It appears, then, that intrathecal therapy may not be indicated and may even be dangerous. The clinical results on the whole have been good. In the entire series,recovery occurred in 24 (60 per cent), and death in 16 (40 per cent), rates which compare favourably with other reports over the past few years. Formerly, patients under 2 years of age had been considered to have a poor prognosis. In this series in 8 patients belonging to this group, there were 5 recoveries and 3 deaths. The recovery date in patients 50 years and over, bears out the poor prognosis previously reported in elderly patients. A higher recovery rate in this series has been attributed to treatment with penicillin supplemented with sulfonamide therapy.

ERIC COELHO.

THE CONTROL OF PRURITUS WITH ADENOSINE-5- MONOPHOSPHATE, Susinno, A. M.: Amer. Pract. 2: 491-499, 1951, 1 table 14 references

The author tried adenosine-5-monophosphate in 66 selected cases of severe intractable pruritus associated with a variety of causes. The pruritus had been present in all these cases at least for 3 weeks and there had been no evidence of spontaneous improvement. The substance used was the sodium salt of adenosine-5 monophosphate (My-B-Den) either in tablet form (sublingual) or by intramuscular injections. In most instances, the tablets were given 60 mg. per day (3 tablets) for 5 consecutive days, in other instances 100 mg. (5 tablets) daily for 3 consecutive days. The tablets were taken at intervals of one hour and required 15 minutes to pass into solution beneath the tongue. No other therapy was employed. The results were considered positive only if medication repeatedly produced a 75 per cent relief of the pruritus within 3 days. Those showing amelioration later than 3 days or a subsidence of pruritus less than 75 per cent, or failed to respond after initially good results,were regarded as failures. In 38, or 57.6 per cent there was repeated dramatic relief and improvement after administration of adenosine-5-monophosphate. Twenty-two or 33.3 per cent failed to respond at all in any convincing fashion. In 6, or 9.1 per cent, the results obtained were lesser and showed varying degrees of relief. Those responding most favourably were patients with varicose ulcers, diabetes, pregnancy and post-partum pruritus, pruritus scroti due to unknown causes, and malnutrition states. Some suffering from pruritus vulvæ, pruritus ani and contact dermatitis showed dramatic improvement, while others reacted negatively. The disease categories in which the results were completely negative were the so-called neurodermatitis, psoriasis, Duhring's disease and senile pruritus. Side reactions were present in 9 cases and tended to diminish or disappear during continued therapy. The toxic reactions complained of were headaches, chills, dizziness, diarrhœa and in a few cases, frequency of urination.

ERIC COELHO.

CONGENITAL MALARIA, Covell, Sir Gordon: Trop. Dis. Bull, **47**: 1147-1167, 1950.

The author has reviewed all published literature about a controversial question of transmission of malaria from mother to child either before or at the time of parturition, and has arrived at the following conclusions:

1. Intra-uterine transmission of malaria from mother to child is a well established fact.
2. The manner of transmission remains a conjecture in spite of a number of theories.
3. Normally, the placenta provides a very effective barrier to the passage of the malarial parasite. Massive infection of the placenta can occur both in non-immune subjects and in those possessing a high degree of tolerance to malaria without the child becoming infected.
4. Congenital malaria can occur without damage to the placenta and infection can pass from mother to fœtus before the onset of labour.
5. Congenital malaria can occur in th absence of any evidence of active malaria in the mother during pregnancy.
6. The form of parasites in which the infection is transmitted through the placenta is not known.
7. It is possible that malaria alters the placental barrier in some form through which transmission occurs, but there is no concrete evidence.
8. Indigenous populations of malarious regions possessing a high degree of tolerance to malarial infection have a low incidence of congenital malaria, but in some areas there were as many as four cases in fifty-four consecutive deliveries.
9. Any of the three species can give rise to congenital malar a.

10. A great degree of passive immunity can be transmitted from mother to child.

11. Malaria in an epidemic form is an important cause of abortion, miscarriage and stillbirth and of deaths among newborn infants. The incidence will vary upon the degree of tolerance to the disease possessed by the mother.

J. C. PATEL.

DIAGNOSIS OF MASKED HYPERTHYROIDISM IN CARDIAC PATIENTS WITH AURICULAR FIBRILLATION, Bortin, M. M. Silver, S. and Yohalem, S. B.: Amer. Jour. Med. **11** : 40-43, 1951.

Auricular fibrillation is caused by thyrotoxicosis and by valvular heart conditions. In hyperthyroidism, auricular fibrillation is a frequent occurrence. In some cases auricular fibrillation may be the only manifestation. The authors have studied 55 cases of thyrotoxicosis in all of which auricular fibrillation was present. In 8 cases (15 per cent) of auricular fibrillation, hyperthyroidism was masked. They were studied by means of radio-iodine excretions and plasma protein-bound iodine determination. The authors point out that thyrotoxicosis should be excluded in all the patients with auricular fibrillation by use of these methods.

J. C. PATEL.

EFFECTS OF CERTAIN ANTISPASMODIC DRUGS ON THE INTACT HUMAN COLON WITH SPECIAL REFERENCE TO BANTHINE (β-DIETHYLAMINŒTHYL XANTHENE-9-CARBOXYLATE METHOBROMIDE), Kern, F. Jr., Almy, T. P. and Stoke, N. J.: Amer. Jour. Med. **11** : 67-74, 1951.

The authors have compared the action of the antispasmodic drugs atropine, trasentine, syntropan with that of banthine, a new synthetic drug, on the intact human colon. It is well known that experiments which are performed on animal colons, and the drugs found effective by such methods, may not be equally effective on human intestines and hence the final trial should always be done on intact human subjects. The authors have devised a method of intubation of the distal colon by a single distensible balloon, 10 cm. in length. The position of the balloon is verified by fluoroscopy. The lower end is connected with a rubber tube to a water manometer which records the changes of pressure in the balloon and consequently in the colon. Five subjects were studied with atropine. They found that atropine had a slight effect and for a short time, on the motility of the sigmoid colon, but trasentine and syntropan had none. The response of the sigmoid colon to banthine ws studied in 37 normal human subjects. 100 mg. was given by mouth and the sigmod motility was completely or almost completely abolished by this drug in between 7 and 45 minutes, usually within 15 minutes. The effect lasted for more than 2 hours. In 15 mg. doses the effect was partial and present in a few cases. In 25 mg. dosage the effect on the colon was less marked. Banthine was given intravenously to five individuals and a dosage of 15-20 mg. showed prompt abolition of sigmoid motility. In doses of 15 to 25 mg., the side effects of banthine were dryness of the mouth and tachycardia in most of the subjects. There was no effect on blood pressure. A few patients had blurring of vision. The authors have come to the conclusion that banthine is unquestionably the potent antispasmodic agent but the amount necessary to affect the colon motility pattern of some patients with irritable colons is more than can be given without producing side effects and hence it may not be a useful drug...Further work is recommended.

J. C. PATEL.

PLASMOSAN : A SYNTHETIC SUBSTITUTE FOR PLASMA, Throwar, W. R. and Campbell H. : Lancet, **1** : 1094-1099, 1951.

Polyvinylpyrrolidone (P.V.P.), one of the colloidal substances, seems promising, to retard the excretion of saliva solutions by the kidneys. It was first used in Germany in 1939-45, but had certain objections. The present preparation is free from objections and contains P.V.P. 3.5 Gm., sodium 361 mg., potassium 22mg., calcium 9 mg., magnesium 0.06 mg., chloride 582 mg., bicarbonate 17 mg., and dissolved carbon dioxide 75 mg. in 100 c.c. This gives a colloidal osmotic pressure nearly that of blood, is isotonic and quite safe.

P. V. P. is a white solid, slightly hygroscopic, water soluble, (with a pH of 4.5 to 7.0), stable, and without any toxic effects, immediate or delayed, when used as a 25 per cent aqueous solution subcutaneously or intramuscularly.

As regards its fate in the body, the authors claim that as much as 75 per cent of P. V. P. content of Plasmosan can be recovered from the urine, without any ill effects on kidney function or any alteration of blood urea and urea concentration test. The authors have described the various methods of estimation of P. V. P. in urine plasma and serum, as also the effect of Plasmosan on whole blood. The clotting time, and bleeding time are unaffected, but the E. S. R. probably shows a rise.

The indications of Plasmosan are those of plasma, and as much as 3,500 c. c. has been given to a patient in one week. The common dosage in man has been about 8 c. c. per Kg. of body weight. It keeps perfectly well, does not require special storage conditions and is cheap. It may be mentioned that the urine findings may be modified during its use, *e.g.*, reducing substances may be present in urine, without any actual sugar, and a false test for albumin may be positive (with trichloracetic acid or Esbach's reagent), but not with nitric acid and heat tests.

V. D. ARORA.

ACTION OF VITAMIN B12, FOLIC ACID AND LIVER EXTRACTS ON THE FREE PROTOPORPHYRIN CONTENT OF RED BLOOD CELLS, Benard, H., Gajdos, A. and Gajdos-Torok, M. : Nature, **167** : 990, 1951.

In anæmia of iron deficiency, the free protoporphyrin in the red cells increases markedly to several hundreds of micrograms per 100 c.c. of red cells, returning to normal (20-40 µg.) on remission of anæmia. In untreated Addison's disease, the concentration of the pigment is diminished but increases considerably under appropriate treatment. This deficiency in pernicious anæmia is thought to be a deficiency in the synthesis of this pigment brought about by the lack of antipernicious factors.

In the authors' experiments with vitamin B12, folic acid or active liver extract, a rapid erythrocytosis was accompanied by a marked erythrocyte hyperprotoporphyrinæmia usually 6-24 hours after injection of antipernicious agents.

They have shown that vitamin B12, folic acid and active liver extract cause, in rabbits, a considerable increase in the free protoporphyrin content of the erythrocytes, similar to that found in the treatment of Addison's anæmia.

The antipernicious anæmia factors, in their opinion, accelerate the synthesis of the pigment. They depleted their rabbits of their reserves of glycine, a material for building porphyrin, by previous injections of high doses of benzoic acid. In animals so prepared, the injection of vitamin B12 or folic acid was followed neither by an erythrocytosis nor by an increased concentration of protoporphyrin in the red cells. The subsequent administration of glycine re-established the normal response to vitamin B12 or to folic acid.

L. K. BANERJI.

CONTINUOUS METABOLISM OF HÆMOGLOBIN IN THE RED CELLS OF PERIPHERAL BLOOD, Benard, H., Gajdos, A. and Gajdos-Torok, M.: Nature, **167**: 989, 1951.

During the treatment of anæmia, the increase of hæmoglobin often lags behind the rise in the number of red cells.

The authors' experiments showed that a single dose of 15 mg. of folic acid or 20 µg. of vitamin B12 in rabbits induces a notable erythrocytosis in 6-24 hours. The hæmoglobin value instead of increasing remains at its initial level with a consequent marked lowering of the colour index.

The increase in the number of red cells and the stationary hæmoglobin value can be explained by the formation of new erythrocytes deprived of, or at least very deficient in, hæmoglobin; but examination of stained smears reveals a homogeneous tinctorial appearance in the red cells and systematic measurements of the red blood cells have shown no difference in mean cell diameter during erythrocytosis.

From these observations, the authors believe that a redistribution of hæmoglobin occurs between old and newly formed red cells, the nature of which is very complex and, no doubt, involves a degradation and resynthesis of the blood pigment operating in the hæmatopoietic organs. At all events, one must consider that the erythrocyte, during the hundred odd days of its normal life, does not possess a fixed and immutable hæmoglobin content; this content can vary, particularly during certain hæmatopoietic incidents.

The protoporphyrin arising from the degradation of hæmoglobin is not utilised as such for the resynthesis of the blood pigment. The rapidity observed in their experimental conditions of the turnover of hæmoglobin during the erythrocytosis requires an intense production of protoporphyrin to accommodate the speed of its resynthesis to the speed of its degradation.

In their experiments, folic acid or vitamin B12 injection was followed in a few hours by a considerable increase in the content in the red cells of free, non-hæmoglobin protoporphyrin.

L. K. BANERJI.

PROBLEMS CONCERNED WITH THE HISTOLOGIC DIAGNOSIS OF TUBERCULOSIS OF LYMPH NODES, McDonald, J. R., and Weed, L. A.: Amer. Jour. Clin. Path. **21**: 223, 1951.

Diagnosis of tuberculosis is more often based upon histologic evidence rather than the demonstration of the organism, *Mycobacterium tuberculosis*. Many pathologists claim that the *Mycobacterium tuberculosis*, produces a specific reaction in human tissues. In the opinion of the authors " this is an unconscious admission on the part of the pathologist on deficiencies in personnel material and space." There are many other agents which at times give rise to histopathologic reactions which stimulate those found in tuberculosis and it is therefore important that if the patient is to have the benefit of the proper treatment a causative agent should be isolated and identified. The authors have reported cases illustrating shortcomings of histologic diagnosis of tuberculosis. The illustrated cases fall into several groups. Group 1. Tuberculosis not suspected on biopsy; bacteriological examination revealed the presence of *Mycobacterium tuberculosis*: Group 2. Tuberculosis suspected on biopsy but other agents found such as Brucellosis and coccidiosis limits. Group 3. Tuberculosis suggested on biopsy but the etiologic agent is not found and in such cases it might not be fair to the patient to make a histologic diagnosis of tuberculosis. Histopathologic diagnosis alone of tuberculosis in lymph nodes is subject to error, as *Mycobacterium tuberculosis* may occasionally be present in lymph nodes in which the histopathologic response is thought to be non-specific

M. V. SIRSAT.

CARCINOGENIC AND TOXIC EFFECTS OF URETHANE IN ANIMALS, Mostofi, F. K., and Larsen, C. D.: Amer. Jour. Clin. Path. **21** : 342, 1951.

The authors describe in the present communication pathologic changes in the lungs, kidneys, female gonads and liver as encountered in experimental animals. Urethane produced adenomas of the lung in mice and rats, regardless of the route of administration. These tumours were of the size of a pin-head or larger and most of them were located in the periphery of the lung. Urethane also interfered with the normal maturation of ovarian follicles and produced glomerular lesions in the kidneys of certain strains of mice. In an experiment, where the authors have given a single intraperitoneal injection of 25 mg. of urethane in aqueous solution; within the first three hours, the liver of a strain of mice appeared to be yellowish and slightly enlarged. Microscopic examination of the liver showed congestion, edema and fatty vacuolization of the hepatic cells. The authors suggest that patients treated with urethane should be studied with reference to possible disturbance of kidney function, menstrual cycle and reproductive activity. If such patients die, these organs and the lungs should be carefully examined if an autopsy is available. Since urethane has induced pulmonary tumours in animals, it may possibly act as a carcinogenic agent in man.

M. V. SIRSAT.

SURGERY

EXPECTANT TREATMENT OF PYOGENIC INFECTIONS OF THE HAND, Gordon, I: B. J. S., **38** : 331-339, 1951.

As the result of an experience of over 2,000 cases of hand infections treated at the casualty clinic of the Victoria Infirmary, Glasgow, the author has come to the conclusion that a more conservative attitude is not only safe but desirable, and that our notions, about the pathological manifestations and principles of treatment so ably described by Kanavel and others, have to be altered.

The author deals mainly with infections of the flexor aspects of the fingers and would like to classify them from the practical point of view into: (1) Pulp infections, *i.e.*, primarily involving the soft tissue overlying the flexor aspect of the terminal phalanx. (2) flexor cellulitis: all infections primarily involving the soft tissues overlying the flexor aspect of the proximal two phalanges. The grouping of superficial and deep infections under the same heading is done advisedly, because, despite earlier teaching to the contrary, it is not always easy to decide on clinical examination whether the tendon sheath is involved or not. The conservative treament was the same whether the tendon sheath was involved or not.

Pathology of Pulp Infections:—Infection of the pulp commences as a soft tissue cellulitis, and if left to its own devices, gradually localises with the formation of a tough slough and this softens with formation of pus and the abscess so formed will point centrally, terminally or laterally in the pulp. Of a total of 431 pulp infections, 101 resolved completely with local heat, rest and penicillin. If the slough formed is removed after being separated largely by natural means, it leaves a clean cavity which is quickly obliterated by re-expansion of the surrounding normal tissue and by healthy granulations. Tension in pulp infections has been said to cause obliteration of the terminal vessels running to the bone from laterally placed digital vessels. If this were true, then increasing density of the bone should have been seen in the roentgenogram, rather than the usual osteoporosis which is the result of hyperæmia. Quite often the lateral incisions placed for drainage precipitated sequestration because they often damaged the already precarious blood supply.

Pathology of Tendon Sheath Infection.—Infection of the tendon sheath has been considered to be an indication for immediate surgery because of the belief that once infection got into the sheath it spread rapidly to the limits of the sheath. It was also assumed that the tension in the sheath could rise to such an extent that the tendon would be deprived of its blood supply. It seems improbable that inflammatory tissue tension could ever be raised above the pressure in the vessels on the arterial side of the capillary lake, which is the force producing the exudate. The clinical picture of a case treated conservatively suggests that upon the entry of infection there is an immediate widespread effusion in the sheath with swelling and tenderness along the line of the sheath and diminished function. The layers of the synovia soon become adherent around the point of entry of the infection, the effusion in the sheath is partly absorbed and an inflammatory barrier is built up spreading from the level of the sheath to the more superficial tissues and skin. If the defence is adequate localisation occurs and pus points eventually on the palmar surface of the finger. The tenderness over the rest of the sheath subsides and function improves. Now is the time for incision, removal of the anterior necrotic wall of the fibrous tunnel and synovial sheath to expose the tendon in the floor of the abscess.

Principles of Treatment :—The author does not agree with the 3 principles laid down by Kanavel, viz., 1) The barriers to the spread of infection in the hand are largely anatomical, 2) incision should be early in the finger even before pus had formed so that tension could be relieved ; 3) incision in the finger for sheath infection should be laterally placed rather than on the palmar aspect. The soundness of the first two principles has already been questioned in the discussion above. His objections to the lateral incision are : a) it provides indirect drainage ; b) it often traverses uninfected tissue, and the inflammatory natural barrier ; c) it often damages the very vessels it was designed to preserve ; d) in passing sinus forceps across the front of the phalanx to open the sheath, the sheath is partially destroyed and the vinculæ carrying the blood supply to the tendon are ruptured ; e) it is not always easy to diagnose tendon sheath infection, and sometimes an uninfected sheath may be opened , f) the lateral incision looses much of its attraction when most of the evils ascribed to palmar incisions and scars are found to be unwarranted from practical experience.

The principles the author annunciates are : (1) The real objective of the defense mechanism is localisation. The patient gets relief only when the infection ceases to spread. This can be observed in the patient who though he still has a big collection of pus in the tissues, declares that pain is gone. (2) Surgery should play no part in actively spreading pyogenic infection in the hand, but should only come in as the scavenger to clear up the debris of the battelfield after the fight has been won by the defences. Early incision devitalises tissue and adds a burden to an already overtaxed blood supply and damages a natural barrier to spread. (3) Drainage when necessary should be direct.

Treatment :—1. Parenteral penicillin. 2. Kaolin poultice (dry) changed once a day. Wet dressings are avoided as they foster bacterial growth. 3. Sedatives. In about 2 to 4 days localisation occurs and this follows on to complete resolution or abscess formation. Widespread pain disappears though localised pain and tenderness remain. While in the first two years surgery was invoked at this stage, latterly such localised collections (unless deeply situated) are left to burst spontaneously, or to be aided in the final eruption by snipping the dead skin as part of the dressing routine without anæsthesia. A slough is often found which is allowed to discharge in a day or two or can be sometimes picked out with a forceps. When an abscess is to be opened it should be opened under general anæsthesia as local anæsthesia and tourniquet induce harmful ischæmia. Incision is directly over the summit of the abscess, and the roof is removed. After removing all sloughs a flavine emulsion dressing is done and left undisturbed for 3 days. If the tendon is exposed, after 3 days it will be found to be covered with granulations. Movements are encouraged as soon as function begins to return soon after localisation.

Wounds on the flexor aspects of the fingers and hands, contrary to popular belief heal rapidly and the scars are pliable and non-tender. The healing time by this conservative procedure is less than after early incision—average 13 days.

E. J. BORGES.

ANÆSTHESIA FOR BRONCHOGRAPHY IN CHILDREN, Mushin, W. A., and Lake, R.: Anæsthesia, **6**: 88-91, 1951.

The author faces the problem whereby a child who must not be frightened, and whose respiratory functions mut not be depressed, must at the same time be in such a condition as to enable the radiologist to instil the radio-opaque oil into the trachea without initiating coughing and to put the child into the various postures necessary for the spread of the oil to all parts. Further the child must soon recover so as to eliminate the oil by energetic coughing.

The authors' debate the problem of local over general anæsthesia but believe that though local anæsthesia, of some degree, for the respiratory tract is essential, unconsciousness is desirable in addition. However, no method of anæsthesia should be used which depresses the cough reflex for more than the required time.

Puncture of the Cricothyroid membrane :—Under a brief general anæsthetic a cruved needle is inserted into the trachea through the cricothyroid membrane; some cocaine solution injected and the child is allowed to wake up, when the oil can be instilled. This method is not favoured by the author.

The "Drowning Technique :—After rapidly and deeply anæsthetising the child a large volume of oil is poured into the mouth and inhaled. Though simple, this carries the risk of respiratory obstruction and upper lobe filling is poor.

Injection of oil through a small bore catheter during endotracheal Anæsthesia :—A small bore catheter is passed through the lumen of the endotrachal tube. Though the endotracheal tube itself would seem to ensure an airway, the author believes that the tube alone causes some reduction in the available airway and in a child with bronchiectasis this could be a grave matter.

Oil-Catheter alone :—The endotracheal tube is dispensed with and a small gum elastic urethral catheter or polythene tubing (2-3 mm. outside diameter) is passed into the larynx. The tube is about 11 inches long with the hub of a record needle inserted into it.

Technique :—Basal anæsthesia is induced with rectal bromethol. A suitable dose of atropine is also administered.

The child is usually so sleepy that laryngoscopy is tolerated or if necessary, trilene by open drop or mixed with nitrous oxide oxygen is used. When the larynx is exposed, one puff of 5 per cent cocaine from a fine atomiser is directed on to it and the oil catheter passed through the vocal cords, for half an inch or so beyond, and fixed with adhesive tape. An injection of 0.5 c.c. of a 2.5 per cent cocaine solution is injected into the catheter followed by an equal quantity of air. In a few minutes when the child settles down under the bromethol anæsthesia he is ready for oil instillation.

EUSTACE J. DE SOUZA.

SUBCLINICAL MINERAL OIL PNEUMONITIS, Schneider, L.: New York State Jour. Med. **51** : 245, 1951.

The author again draws attention to a disease that is often mistaken for cancer of the lung and other lung diseases. Though lipid pneumonitis in marantic children and debilitated aged adults has been known for many years, it is not generally known that normal adults who take liquid paraffin daily are also exposed to this disease. The disease may also arise as the result of frequent liberal instillations of mineral oil nose drops. There are at least 3 nose-drop preparations in a mineral oil menstruum being widely used to-day.

As chest fluoroscopy is being widely used as a routine investigation now-a-days the danger of mistaking lipid pneumonitis for more serious diseases is great. The author describes one case where a localised rounded opacity in the right lower lung was mistaken for a carcinoma and the lobe resected by the surgeon. There is danger that the enthusiastic chest surgeon in an attempt to operate on cancer of the lung in its earliest stages might mistakenly remove the entire lobe or lung.

The diagnosis depends upon three factors: (1) The history of a liberal use of mineral oil by mouth or by nasal instillation, (2) The X-ray findings, (3) the examination of the sputum for oil droplets.

The history :—The majority of apparently healthy adults in whom the lung lesion is accidentally uncovered by chest screening are found to have absent or markedly diminished gag reflexes. Many of them drink the oil straight from the bottle; those that develop the disease after nasal instillation are usually in the habit of tilting the head well back so that the oil trickles into the pharynx.

X-ray findings :—No pathognomonic signs are known. However, two types of lesions are produced. A diffuse process is more commonly seen. It may appear as an ill defined, veil-like basal haze which gives the involved portion of the lung a " dirty " appearance roentgenographically. This sort of lesion when small may be missed on the ordinary inspiration film, but will be brought out by taking a film in expiration. At times the diffuse process is seen as a fine conglomerate fibrosis that streaks or smudges from the heart border across the base, soon to disappear in normal parenchyma and often extending clear across to the periphery of the lower portion of the lung field.

The less frequently seen circumscribed lesion may vary in size from a few millimetres in diameter to a sharply outlined mass of several centimetres. This is called a paraffinoma and is the type most likely to be mistaken for a neoplasm. Unlike primary or metastatic malignant lesions, the paraffinoma is usually surrounded by interlacing fibrosis and is not accompanied by regional adenopathy.

Sputum Examination :—The clinching criterion in the diagnosis is the finding of mineral oil droplets in the sputum, or after lung aspiration through the chest wall. It is important to stop the intake of oil for several days before the sputum sample is taken, and it is also wise to have the patient gargle before expectorating the requested specimen.

E. J. BORGES.

THIRD VENTRICULOSTOMY IN TREATMENT OF OBSTRUCTIVE HYDROCEPHALUS IN CHILDREN, Voris, H. C.: Arch. Neurol. and Psychiat. 11 References. **65**: 265-217, 1951.

In the author's experience the ratio of obstructive hydrocephalus to communicating hydrocephalus is about 2: 1, and in the former variety, if the obstruction can be relieved or circuited the progressive enlargement may be brought under control.

He discusses the various causes of obstruction and the treatment.

The Arnold-Chiari malformation is usually associated with spina bifida especially the myelocele. The medulla is elongated, and the lower end of the fourth ventricle and cerebellar tonsils are below the level of the foramen magnum. The mechanism has been explained by Lichenstein as being due to the abnormal attachment of the cord or membranes to the surrounding and overlying tissues, which may exist, though not usually, even in spina bifida occulta.

Inflammatory obstruction are common, at the aqueduct, fourth ventricle or cerebello medullary cisterns and even the basal cisterns. The latter are often the chief site of block in meningitic hydrocephalus where no surgical remedy is possible except ventriculo-ureteral anastomosis. The post-meningitic hydrocephalus which was formerly confined to those who survived epidemic meningococcic meningitis, or the terminal stages of tuberculous meningitis, now is a complication of the other varieties of meningitis since the advent of modern chemotherapy.

Neoplams though not common under two years do occasionally occur and cause obstruction. The author advises the dye test unless there is an associated spina bifida where the sub-arachnoid space may be obliterated, but a preliminary sub-dural tap should precede the test to rule out a sub-dural hæmatoma. He also stresses the value of ventriculography especially in tumours of the third ventricle, which may have to be followed by exploration of the posterior fossa.

When this latter procedure is carried out, the Torkildsen operation is an obvious answer for the relief of hydrocephalus, but is temporary in inflammatory conditions as there is usually a tendency to adhesions of arachnoiditis and obliteration. Though sub-occipital decompression and opening of the fourth ventricle has been advocated the author finds the mortality in infants disturbingly high. To obviate this he tries to establish free communication between the third ventricle and peduncular cisterns.

At first the transfrontal route of Stookey and Scarff was used. This was useful in older children but not in infants. Therefore the lateral approach of Dandy was used, and the floor of the third ventricle punctured and the opening carefully enlarged.

The author reports in detail his first case on which this procedure was successfully carried out and the follow-up 40 months after operation.

EUSTACE J. DE SOUZA.

POST OPERATIVE URINARY RETENTION, Dick, V. S.: Surg. Clin. North America, **31**: 691-695, 1951.

The importance of this common condition is stressed especially to bring home the fact that it may become so serious as to overshadow the very condition which originally required surgery.

Seen following surgery in both sexes and at all ages it is most common in the prostatic age in the male, and in the female is most common after gynæcologic procedures. The tense, nervous, imaginative patient is often the one to develop it regardless of the site and nature of the operation, while there is no doubt also that the magnitude of surgical procedure, type and duration of anæsthesia, narcotics and other medications, all play their part in post-operative retention.

The post-operative position of the patient, the amount, type and rate of administration of intravenous fluids and other fluid losses all warrant close attention.

The author recognises the difficulty males encounter in voiding urine in the recumbent position and advises that where complete bed-rest is faced after an operation it is wise to get the patient pre-operatively to pass urine in this position.

Over distension of the bladder in a patient who is partially anæsthetised or narcotised will result in a decrease in bladder tone for some days even if the bladder has been subsequently catheterised. Drugs of the cholinergic type have been of some help in the prevention and treatment of post-operative urinary retention. Prostigmine given pre-operatively and continued post-operatively has been of some aid and recently urecholine has been used. It may be given orally or by subcutaneous injection but not intravenously or intramuscularly. The use of 5 mg. subcutaneously, repeated in thirty minutes for a total of 3 doses has been very effective. Its use should not be delayed till the bladder is over distended. The contra-indication and individual suceptibility to these drugs must of course be carefully noted.

Intermittent catheterization for post-operative retention should be designed to avoid over distension and at the same time to catheterize as few times as possible. It must naturally be regulated by noting the water balance and by watching the individual needs of the patient. If there is any question as to the complete emptying of the bladder it is far better to check the residual rather than to allow him to gradually become overdistended.

The author has found that in some patients the injection into the bladder of a slightly irritant solution like 0.5 per cent mercurochrome, following catheterization is useful, but must be promptly abandoned if any discomfort results. Where intermittent catheterization is poorly tolerated or where a considerable time is likely to elapse before normal micturition will be resumed, the use of an indwelling catheter is advisable. After insertion it should be connected with a closed sterile irrigating system with irrigations every three hours during the day. As some degree of bladder infection and urethritis is bound to occur, it is wise to give a urinary antiseptic in small doses, and to check the urine sufficiently following the resumption of normal micturition till all infection has cleared.

Ordinarily the indwelling catheter is removed when the patient becomes ambulatory but unless there is prompt voiding of adequate amounts, catherization for residual should be carried out to prevent over distension. It is particularly necessary to check for residual after perineal plastic surgery, since often, voiding is resumed but a fairly large residual later causes trouble after the patient has left hospital.

Patients who have undergone surgical removal of the rectum are often prone to retention due to disturbance of the nerve supply. Here the same principles apply, only, endoscopy and transurethral resection of the prostate if indicated should be resorted to early. It is here, also, that the parasympathetic stimulating drugs are of considerable help, where there is evidence of a neurogenic element and mechanical obstruction has been eliminated.

EUSTACE J. DE SOUZA.

ATTEMPTS AT THE EXPERIMENTAL PRODUCTION OF PORTAL HYPERTENSION, Douglass, T. C., Mehn, W. H., Lounsbury, B. F., Swigert, L. L. and Tanturi, C. A.: Arch. Surg. **62** : 785-788, 1951. 15 refrences, 2 tables, 1 fig.

From the work of Von Eck, Pavlov and Freeman it seemed that a porto-caval fistula with ligation of the portal vein between the liver and the anastomosis would remain patent.

The authors found that such a fistula without portal obstruction results in closure of the fistula in approximately one-third the cases in three to six weeks.

A survey of the literature revealed that chronic portal hypertension without impairment of the caval system has been produced in the dog only by Rousselot and Thompson, who produced cirrhosis of the liver with splenomegaly and submucosal œsophagial varices by the injection of silicon dioxide into the splenic vein. The authors have attempted to produce a chronic portal hypertension by partial occlusion of the blood vessels entering and leaving the liver, under intravenous sodium pentobarbital anæsthesia. The normal pressure varied from 10-15 cm. of water. Goldblatt clamps were used on the portal vein to partially obstruct its lumen, and also on the hepatic artery. There was no increase in portal pressure two to six weeks later, no dilation of the vein and an adequate venous collateral circulation was present.

In two animals the portal vein was then completely occluded, with no change in the animal and no increase of portal pressure.

When the portal vein only was completely occluded in one stage, all the animals died promptly. In a third group of seven dogs, the Goldblatt clamp was placed on the portal vein and gradullay tightened till the portal pressure doubled; three died in 24 hours and one after 16 days. The remainder, three months later, revealed normal portal pressure, which dropped below normal when a porto-caval anastamosis was performed.

To see the part played by anærobic infections, Tanturi administered 300,000 units of penicillin to five dogs where the portal vein was completely occluded by silk ligatures. Postal pressures varied from 30-52.8 cm. of water after occlusion. One dog died of uncontrollable hæmorrhage, and 3 others within 24 hours, with splenic congestion. In the fifth which survived, and was killed a month later, a small pancreatic branch had been missed and had become enormously dilated. In the fifth series, clamping the main hepatic vein as it enters the vena cava failed to produce cirrhosis or increased portal pressure or varicosities.

EUSTACE J: DE SOUZA.

MANAGEMENT OF CARCINOMA OF THE PROSTRATE, Harrison, J. H. and Poutassee, E. F.: Amer. Jour. Med. **11** : 55-66, 1951.

The authors have studied 100 patients with carcinoma of the prostrate during a four perid 1946-49. Radical prostatectomy was performed in 19 patients and only simple prostatectomy in 29. Hormonal treatment alone was administered to 47 and 5 patients received no treatment. They were of the opinion that early diagnosis followed by radical prostatectomy and hormonal therapy will improve the results. The most effective hormonal treatment consists of orchidectomy combined with estrogenic therapy. This hormonal treatment should be used in all cases, including those having radical prostatectomy, because of the possibility of antecedent unrecognised metastatic spread, either local or remote. Primarily, hormonal treatment is usually effective in causing local regression and sometimes it might help to promote operative removal.

J. C. PATEL.

A CRITIQUE OF FAT EMBOLISM, Whitson, R. O.: J. Bone and Joint Surg.: 33A: 447-450, 1951. 13 references.

The author makes an attempt to correlate the clinical signs and symptoms of so-called fat embolism with our present-day knowledge of traumatic shock.

The diagnosis has been made in a variety of conditions and fat embolism has been named the cause of death. The commonest initiating factor has been injury to long bones usually multiple and severe. Burns, contusions and difficult labour and even incisions in the adipose tissue of obese subjects has been blamed. Among the non-traumatic conditions as a cause are, pneumonia, acidosis, hepatitis, chronic tuberculosis. Lehman and McNattin reported fat embolism in about half the lungs of fifty unselected autopsy specimens, where probably they are coincidental with anoxæmia. The author stresses that where one would expect fat embolism, as in medullary pinning, it is rare, as also in tibial bone grafting. While it is reported in other orthopædic procedure, in most of these cases the patient was either a poor risk, or the procedure shocking. In healthy individuals with good pre-operative and post-operative care it does not occur following reconstructive surgery of the skeleton. The pathology is believed to be that fat enters the venous system at the site of injury and is carried to the lungs and brain.

The author believes that blood and fat extravasated cannot re-enter the circulation as the walls of the vessel collapse and are not kept open as was thought by Gauss. Crystalloid solutions including dyes may enter the circulation but they do so by dialysis and staining of the lungs by dyes injected into the hæmatoma is not proof that fat globules behave similarly.

Lehman and Moore have reproduced the picture of fat embolism by pushing ether inhalation to death. Also another experiment with intravenously injected fat led to the conclusion that if man has the same circulatory susceptibility to circulating fat as dogs, there is not sufficient fat in the femur to produce death. For a diagnosis of fat embolism the lungs must be found to be the seat of major changes.

Further, autopsy changes found in shock are identical to those attributed to fat embolism.

Phemister and Læster have demonstrated that a large part of the blood volume may be lost into the tissues of the site of a closed fracture.

Regimens of therapy towards removing the fat globules from the blood stream have been uniformly unsuccessful. The plan of treatment should be rather for the prevention and alleviation of shock, prevention of blood loss and care against anoxæmia.

EUSTACE J. DE SOUZA.

PEDIATRICS

CONGENITAL DUODENAL OBSTRUCTION, Krafft, C. J., *et al.*: J. Ped. 37: 44-50, 1951. 4 figs, 18 references.

Duodenal obstruction is rare, the incidence is said to be 1 in 20,000 live births; no preferences for sex or hereditary influences are noted, though it occurs more often in premature infants. Most infants are normal at birth and begin vomiting within the first 36 hours or shortly after feeding is instituted; vomiting gradually becomes projectile, and bile is present in the vomitus if the obstruction is after the ampulla of Vater. Meconium stools are usually passed. Progressive weight loss with dehydration occurs. Physical examination reveals weight loss and dehydration depending on the duration of symptoms; peristaltic waves traversing the epigastrium may be seen. Frequently there is fullness of the epigastrium with tympany, while the lower abdomen is scaphoid and dull to percussion. Because plain roentgen films of the abdomen taken within the first 12 to 24 hours are usually inconclusive, Mellins and Milman advocated aspiration of the stomach followed by insufflation of air in sufficient quantities; in tis way the roentgenogram reveals a stomach bubble and a large bubble in what appears to be a dilated segment of proximal duodenum with absence of gas elsewhere in the gastro-intestinal tract. Barium suspensions are contraindicated as being dangerous. Farber's test for epithelial cells in the meconium is relatively unnecessary since the diagnosis with the above criteria will be complete. When diagnosis is established, surgery must not be delayed; the child withstands surgery better within the first 48 hours than a week or so later. Pre-operatively, dehydration and electrolyte imbalance should be corrected by intravenous fluids and blood transfusions supplemented by vitamin K and calcium injections; the stomach is washed, aspirated and the tube left in place during surgery. The type of operation preferred is a duodenojejunostomy rather than a gastro-enterostomy, since the latter causes loss of appetite and failure to gain weight properly. Post-operatively intermittent, stomach aspiration is desirable; parenteral fluids including electrolytes are given in adequate amounts to replace fluid loss and maintain caloric intake.

The authors describe two cases diagnosed on the above lines and treated surgically by gastroenterostomy. Though both infants recovered, they agree that duodenojejunostomy may be superior to gastroenterostomy as post-operative difficulties regarding weight gains, etc., were met with in both their cases.

F. A. NAZARETH.

T WAVE CONTOUR IN THE PRECORDIAL LEADS DURING CHILDHOOD, Reynolds, R. W.; Pediatrics **7**: 400-407, 1951. 2 tables, 2 figs. 1 chart, 18 references

The author studied the T wave in the precordial V leads in 187 normal children and young adults in the age range of 2 weeks to 20 years and in 164 individuals of like age with cardiovascular disease or with disease or medication capable of affecting the cardiovascular system.

In the normal series, between the age of 2 weeks and 7 years, the wave in V2 in the majority of cases was inverted; however, the frequency of notched or diphasic complexes increased as the age of 7 years was approached; between the ages of 8 and 14 years inverted T waves in V2 were less frequent and upright complexes more commonly noted, the latter particularly after age 14. Similar trends were noticed in V4 but at earlier ages; no inverted T waves were found after the age of 3 years; upright T waves in V4 were present as early as at the age of 2 weeks in contrast to an upright T wave in V2 which was noted only after the age of 8 years. In V5, inverted T waves were not seen normally and diphasic complexes were not found after the age of 4 years, while in V2 such complexes were observed even at the age of 20 years. In the abnormal series, many patients had no demonstrable cardiovascular disease and had therefore completely normal electrocardiograms. However, a wide variety of T waves in all leads and at all ages was found, showing marked deviation from the orderly trends found in the normal series; unlike the normal series, in the abnormal series it was not unusual to find the normal transition from inverted to upright T waves, unexpectedly reversed in going from V2 to V6.

Until proved otherwise, the author considers as abnormal: (1) an upright T wave in lead V2 or leads further to the right in children between 2 weeks to 9 years, (2) an inverted T wave in V5 and V6 at any age (3) a reversal or interruption in the normally expected negative to positive T wave from the right to the left precordial leads. He views with suspicion inverted T waves in V4 in patients over the age of 3 years, and diphasic or notched complexes in V4 or V5 after the age of 12 and 3 years, respectively.

F. A. Nazareth.

VENEREAL

One injection schedule for the treatment of early syphilis, Rodriguez, J., *et al.*, Amer. J. of Syph., Gon., and Venereal Diseases, **35** : 246-251.

In January 1949 the authors undertook to fulfil the dream of "Therupia Sterilisans Magna" by adopting one-injection schedule for the treatment of early syphilis. This schedule also helped to relegate the as yet unsolved problem of outpatient treatment lapse, to medical history.

In all 71 patients of early dark-field positive syphilis were treated. Out of 71, fourteen were seronegative primary cases, 21 seropositive primary cases, and 36 were secondary syphilis cases.All the 71 patients were treated with one schedule *viz.*, 2.4 million units of crystalline procaine penicillin G in peanut oil with 2 per cent aluminum monostearate were given intramuscularly in injections of 600,000 units at four different sites.

The authors have discussed the subject under the following heads : (i) effects on syphilis lesions, (ii) penicillin blood levels, (iii) penicillin cerebrospinal fluid levels (iv) comparison of results with other more prolonged schedules. At the end of 6 to 7 months' follow-up period, the authors arrived at the following conclusions : (i) The cumulative percentages of treatment results revealed 70.0 per cent clinically and serologically negative ; 21.7 per cent 3 Kahn units or less ; 6.6 per cent 4 Kahn units or more ; and 1.7 per cent relapse. (ii) when compared with more prolonged schedules (4.8 million units in 8 days and 5 million in 10 days) no significant differences were noted, for the same period of post-treatment observation, both regarding satisfactory results and failure rates. Satisfactory results meant clinical and serological negativity (Kahn titer 3 units or less). Failures signified clinical evidence of failure or serologic reversal patterns plus patients with 4 Kahn unit levels or over. Thus one injection schedule had a definite favourable therapeutic effect in early syphilis comparable to that of the two other more prolonged penicillin schedules. (iii) No serious reactions were observed. Febrile Herxheimer reactions occurred in 25 of 71 patients. Only one patient had tenderness and induration at the site of injection 10 days later. (iv) Effective blood levels of penicillin were maintained for 100 per cent of the patients for 96 hours following the one injection schedule. No penicillin activity was observed in the C.S.F. at the end of the third, twelfth and twenty-fourth hours of injections ; (v) though preliminary results are encouraging, continued studies are necessary to determine effectiveness of this one injection schedule after longer periods of observation.

T. K. Mehta.

Circumcision and Primary Syphilis, Hand, E. R. and Nelson, M. C. : Arch. of Derm. and Syph. **63** : 504-505, 1951.

Brietenstein *in a study of 15,000 circumcised African soldiers and 18,000* European soldiers, many of whom were uncircumcised, observed that syphilis was commoner in the uncircumcised. In 1885 Johnathan Hutchinson first noted that syphilis was uncommon in Jews.

The authors carried out their study on 136 soldiers which included 78 whites, 3 Mexicans and 56 Negroes. They confirmed the above observation and concluded that primary syphilis on the distal end of the penis where the presence or absence of the prepuce could affect the acquisition of syphilis, is rare in circumcised people.

T. K. MEHTA.

CHLOROMYCETIN (CHLORAMPHENICOL) IN THE TREATMENT OF VARIOUS TYPES OF SYPHILIS, Romansey, M. J., *et al.* Amer. J. of Syph., Gon. & Ven. Diseases, **35** : 234-239, 1951.

The present study was started in May 1949. In all about 103 patients of various types of syphilis were treated with chloromycetin by mouth on various-time-dosage schedules. Some of the these treated cases were followed up both clinically and serologically for five to six months after the treatment was over. The time-dosage schedules and results are well brought out in tabular forms.

It was observed that following a single dose of 500 mg. of chloromycetin, the lesions of primary and secondary syphilis in some cases were cleared of spirochetes in 48 hours. The period was reduced to 22 to 28 hours when daily oral doses of chloromycetin were administered in 30, 60 and 120 mgm. per kilogram body weight per day in 6 doses at 4 hour intervals.

The authors have discussed the effect of chloromycetin in various stages of syphilis including neurosyphilis and syphilis in pregnant women but excluding cardiovascular syphilis. They arrive at the following conclusions : (i) chloromycetin, within the limits of the present follow-up (5 to 6 months), appears to be an effective oral antisyphilitic agent ; (ii) chloromycetin dosage of 60 mg. /Kg. /day for 6 to 8 days appears to give the most favourable results of the various treatment schedules tried ; (iii) it is advisable to give the antibiotic for at least 15 days in neurosyphilis and (iv) the small single oral dose (1 to 3 Gm.) curative for gonorrhœa will mask concomitantly acquired syphilis and therefore such patients must have the same post-treatment observation as after penicillin, *i.e.*, from 4 to 6 months.

Reactions to the drug were generally infrequent. Dry mouth and mild diarrhœa occurred only occasionally. Jarisch-Herxheimer reactions of a mild nature manifested by 1° to 2° F of fever were observed in several patients. Glossitis and pharyngitis returned to normal on vitamin B complex treatment.

T. K. MEHTA.

EFFECTIVENESS OF PENICILLIN IN PREVENTING CONGENITAL SYPHILIS WHEN ADMINISTERED PRIOR TO PREGNANCY, Cole, H. N. et al. : J. Ven. Dis. Inform. : **31** : 201-203, 1950.

The present study is based on the results of 341 pregnancies in patients treated for syphilis prior to conception with total dosage of aqueous penicillin varying from 600,000 to 9,600,000 units. 58 of these received simultaneous treatment with arsenic and bismuth. Of 341 women, 321 had primary or secondary syphilis and 20 had early latent syphilis, *i.e.*, all had acute or infectious syphilis.

Results of pregnancy in these women were divided into two groups. Group A consisted of 263 outcomes of pregnancy among mothers who were not pregnant when originally treated. In this group there were 253 live babies and 10 fatalities (abortions, miscarriages, still births and neonatal deaths). Group B. comprised of 78 outcomes of pregnancy among those mothers who had received anti-syphilitic treatment during an earlier pregnancy. In the latter group there were 72 live babies and 6 fatalities. The fatality rate of both groups comes to 49.2 per 1,000 live births. The authors point out that this is lower than the still birth rate for New York City in 1944 which was 80.8 per 1000 live births. On this comparison the authors feel that it is safe to assume that most of the 16 fatalities in this study were not due to syphilis.

For evaluation purposes, the babies in both groups were classified according to clinical and serologic status, as follows: (1) confirmed non-syphilitic: live babies with negative serologic results after at least 90 days of life. (2) Confirmed syphilitic: diagnosis of syphilis established by clinical and serologic evidence (3) unconfirmed: those whose status could not be established. On the basis of these criteria, the status could be established in 229 of the outcomes of pregnancy: 193 in group A and 35 in group B. Of these only one infant had definite congenital syphilis and belonged to group A, i.e., only 0.4 per cent of 229 infants, had congenital syphilis. There appeared to be no difference in the outcome of pregnancy between those women treated during a previous pregnancy and those women treated when not pregnant.

T. K. MEHTA.

TREATMENT OF GONORRHŒA WITH CHLORAMPHENICOL (CHLOROMYCETIN); Greaves, B. et al., Journal of Venereal Disease Information, **31**: 261-263, 1950.

In order to study the value of chloromycetin in gonorrhœa, it was administered to 96 male patients with acute gonorrhœal urethritis. Diagnosis was made by smears and cultures as well. 75 of 96 patients were givn a single oral dose of 750 mg, 16 were given 500 mg., and 250 mg. to the remaining 5 patients.

In order to study the clinical effect, spreads were made from the discharge of 16 patients treated with 500 mg. single oral dose of chloromycetin, hourly for 6 hours. There was no change during the first 2 hours. At the end of 6 hours, no gonococci were detected.

As for the result of the treatment, 96 per cent of those patients receiving 750 mg. of the drug were cured. Of those getting 500 mg., 75 per cent were cured, and of those receiving 250 mg., 25 per cent were cured.

The criteria of cure were the disappearance of symptoms and three negative smears and cultures over a period of 7 to 10 days. Finally, the authors recommend chloromycetin as an effective drug for the treatment of gonorrhœa in 750 mg. single oral dose.

T. K. MEHTA.

STREPTOMYCIN TREATMENT OF GRANULOMA INGUINALE, Pariser et al. Arch. of Dermat. & Syph.: **62**: 261-264, 1950.

Seventy-six patients with granuloma inguinale were treated with streptomycin. Over 60 per cent of them were observed well over 6 months after an initial course of streptomycin. The following criteria were used for including patients for this study: (1) The clinical diagnosis was accepted only if Donovan bodies could be demonstrated in lesions (2) other venereal diseases were treated adequately before starting streptomycin for granuloma inguinale. It was noted that lesions of granuloma inguinale did not show any signs of healing while other venereal diseases were being treated.

The dosage scheme was as follows: 0.6 Gm. of streptomycin every four hours (3.6 Gm. per day) for a total of 18 Gm. of streptomycin. During the course of observation, it was noted that there does not appear to be any relationship between response to treatment and the extensiveness or duration of the disease. Similarly, age, sex and previous treatment appeared to have no influence on the outcome of the treatment. Of the 76 patients treated, 61 responded satisfactorily to one course of treatment as outlined above. 12 patients were retreated because they failed to respond to the first course after several days of observation and Donovan bodies could still be demonstrated in lesions. Three patients (remaining 3) relapsed after complete healing. Donovan bodies were found in the relapsed lesions. Retreatment consisted of 4 Gm. of streptomycin daily for 10 days, *i.e.*, a total of 40 Gm. of streptomycin; out of these 15, three failed to respond to the second course of treatment. One of these was given a third course of streptomycin, consisting of 4 Gm. daily for 10 days and then followed by the oral treatment with 250 mg. of aureomycin every six hours for 8 days, (*i.e.*, a total of 8 Gm. Even after this the case did not improve and Donovan bodies persisted so the patient was then treated with Fuadin. Lesions healed only to recur a month later. The second patient who failed to respond to second course of streptomycin was satisfactorily treated with 2 Gm. of aureomycin a day for 8 days. No recurrence after a month. The third unsuccessful patient was treated with chloromycetin but he had not been followed long enough to judge the effect of treatment.

T. K. MEHTA.

A SIMPLE STAIN FOR DONOVAN BODIES FOR THE DIAGNOSIS OF GRANULOMA INGUINALE; Greenblatt, R. B., *et al*, American J. of Syph. Gon. and Ven. Diseases, **35**: 291-293, 1951.

In 1949 Greenblatt used pinacyanole dye for staining *Trichomonas vaginalis*. It was soon found useful for Donovan bodies as well.

Technique. (i) obtain a piece of clean granulation tissue with the aid of a biopsy-punch. Make smears with the cut surface (*i.e.*, under surface) of granulation tissue. Thus superficial contaminants are avoided. (ii) after the smear has dried flood the slide with a 1 per cent solution of pinacyanole dye in methyl alcohol. Let it act for 1½ to 2 minutes. Then dilute the stain by pouring an equal amount of neutral distilled water, which is allowed to act for a further 1½ to 2 minutes. Wash with distilled water and examine under high, dry and/or the oil immersion lens for Donovan bodies.

The Donovan bodies are found in the large monocytes. The capsules of Donovan bodies stain a purplish pink, and the nuclei a dark blue. Pathognomonic cells (large monocytes with cytoplasmic cysts filled with Donovan bodies) are more frequently found in smears when obtained in the above manner. In tissue section the pathognomonic cell is easily recognized when stained with Delafield's hematoxylin. The capsule of the Donovan body has an affinity for silver salts and in tissue sections may be readily demonstrated by the Deiterle silver stain.

The authors have found pinacyanole method simple and valuable. One photograph showing the punch-biopsy technique and two photographs showing the Donovan bodies in large monocytes (stained by pinacyanole) are included in the text.

T. K. MEHTA.

SKIN

RESIN OF PODOPHYLLUM IN TREATMENT OF MOLLUSCUM CONTAGIOSUM: Sherwood, W., Barefoot and Greensboro, N. C.: Arch. of Derm. and Syph., 63: 256-259, 1951.

It is not always possible to resort to destructive measures for treating molluscum lesions which are often too many and in patients who are non-co-operative because of pain caused by the procedure. For such cases the authors advise topical application of 20 per cent resin of podophyllum in 95 per cent alcohol.

The authors have given a detailed report of a successfully treated case and make mention of two more. The treatment is simple, safe and effective without causing any discomfort or sequelæ. It took about 4 months for complete disappearance of lesions in the first case on weekly application of the resin paint. In subsequent cases the paint was applied on alternate days and the period of healing was reduced to about a month or so.

T. K. MEHTA.

ORAL ADMINISTRATION OF AUREOMYCIN IN TREATMENT OF CERTAIN DERMATOSES; Grurul, J. L.: New England J. Medicine, 242: 928-930, 1950.

Aureomycin was used as the only therapeutic agent by the author in the treatment of some dermatoses which were resistant to other modes of treatment. It was employed on the following dosage scheme: 2 capsules (50 mg.) every 4 hours; when distinct clinical improvement was noted dose was reduced to 250 mg. (1 capsule) every 4 hours four or five times daily; later as lesions subsided almost entirely, a maintenance dose of 250 mg. was given daily. Distinct improvement usually occurred after about seven days. There were no toxic effects necessitating interruption of treatment.

Aureomycin was a failure in (i) 3 patients of chronic discoid lupus erythematosus, (ii) 2 cases of recurrent herpes simplex and in (iii) 3 patients with dyshidrotic eczematoid dermatitis. Comparatively prompt and satisfactory results were obtained in 2 patients of bullous erythema multiforme, whilst a third patient failed to improve.

Good results were obtained in the following conditions; in (i) three of four cases of dermatitis herpetiformis, (ii) nine with sycosis vulgaris, (iii) one with lupoid sycosis vulgaris and (iv) six with Darier-Ravant-Ramel seborrhœic dermatitis.

T. K. MEHTA.

EARLY PROGNOSIS OF LUPUS ERYTHEMATOSUS DISCOIDES, Cochrane, T.: Arch. of Derm. and Syph. 63: 323-327, 1951. 2 tables.

The author has described a 'simple' method of giving prognosis in cases of lupus erythematosus discoides. It depends upon a combination of two factors: (i) Erythrocyte sedimentation rate (E.S.R.) and (ii) clinical appearance of a given case.

The E. S. R. was calculated in 83 cases of lupus erythematosus (L. E.) with 80 cases of miscellaneous dermatosis serving as controls. Cases were divided into three groups A, B, and C according to the E. S. R. Group A consisted of cases with normal E. S. R., *i.e.*, 1-10 mm. in 1 Hr. Group B having an E.S.R. between 10 and 30 mm. in 1 Hr. and group C with an E.S.R. of more than 30 m.m. in one hour. A total of 66, (*i.e.*, 79.4 per cent) of 83 L.E. cases gave abnormal results whereas in the control series 63, (*i.e.*, 78.7 per cent) of 80 cases had their E.S.R. within normal limits.

Clinically L. E. cases were divided into two distinct categories: (1) seborrhœic-like lesions, dull, erythematous, infiltrated patches of indolent appearance with raised and apparently inactive non-spreading edges, the centres of the lesions being irregular, depressed and covered with thick, yellowish-grey or white adherent scales and (2) erythematous lesions, bright erythematous areas of active appearance, the borders of which are well defined and which, although slight induration may be present, have no thickening or raising of the edges, while the centres are smooth and shining and widely dilated follicles are a prominent feature, usually with no or slight scaling.

Treatment of these L. E. cases was carried out with sulfatriad and mapharside. The former for cases with evidence of focal infection and the latter for cases with a tuberculous connection. Results of treatment can be better appreciated from the following table:

	Group A		Group B		Group C	
Clinical type of lesion	Erythematous	Seborrhœic				
Total cases	12	5	33	24	5	4
No. cured	9	..	16	16	..	..
No. decidedly improved	3	..	12	3	1	1
No. of treatment failures	..	5	5	5	4	3
E. S. R.	Normal (1 to 10 mm. in one hour)		Abnormal (Bet. 10 & 30)		Decidedly pathological (above 30).	

From the above table the author draws the following prognostic conclusions:

(1) Prognosis is poor in clinically chronic, (*i.e.*, seborrhœic) cases with normal E.S.R. (group A).

(2) Prognosis is poor in L. E. cases with E.S.R. more than 35 mm. in the first hour, irrespective of clinical type. (group C).

(3) Prognosis seems to be good in erythematous lesions with normal E.S.R. (group A).

(4) Prognosis is good in seborrhœic type of cases with moderately raised E.S.R. (group B) in spite of clinically chronic appearance of lesions.

(5) From the comparison of percentage results in erythematous cases in group A and group B it would seem that the lower the E.S.R. the better the chance of cure.

E.S.R. was performed twice before starting treatment and then on two or more occasions, 8 weeks after the start of treatment.

From the above considerations the author feels that (1) E.S.R. can be used as a reliable guide to the state of the activity of the lesions; (2) when correlated with clinical appearances of lesions, it can give an early indication of the prognosis of the disease; and (3) in satisfactorily treated cases, this test may be used as a means of detecting, treating and perhaps minimizing an early relapse of the disease.

T. K. Mehta.

A. C. T. H. in Dermatomyositis, Williams, A. A. and Bowled, D. P.: Lancet, **260**: 1053-1054: 1951.

Dermatomyositis is classified as one of the collagenoses. Its etiology is still obscure. Dowling thought it to be due to some thyroid disturbance. Infection was considered as a probable cause by O'Leary as culture of the affected muscle during an acute phase has revealed streptococci, staphylococci or both and occasionally a vaccine made from the organisms cultured does bring about improvement. Selye holds that dermatomyositis is one of the many manifestations of the adaptation syndrome and that it responds to adrenocorticotropic hormone (A.C.T.H.)

The authors report a successfully treated case of a married woman aged 34. She was admitted to hospital for pain in chest and dyspnœa. She had dysphagia also. An irregular pyrexia was noted in the hospital besides attacks of swelling of muscles of forearms together with an erythematous rash of overlying skin. The patient had two attacks of the periorbital œdema showing the classical heliotrope eyelids of dermatomyositis (O'Leary). She had lost 28 lbs. weight during 18 months. The rectus abdominis and intercostal muscles were rigid and hampered respiration. Lungs were clear but there was decalcifying osteoporosis. E.S.R. (erythrocyte sedimentation rate) was 25 mm. in 1 hour (Wintrobe). Muscle biopsy from the rectus confirmed the diagnosis.

A. C. T. H. was administered in 7 mg. doses four times a day for a week Pulse and fever were controlled. However on discontinuing the treatment after a week, both relapsed. Thereupon A.C.T.H. 8 mg. *b.d.* was given on four days a week for a further month till a total of 500 mg. was given. With this treatment pulse rate and fever were controlled. A month after the treatment the patient gained 20 lbs. Vital capacity improved from 680 cc. to 1200 cc. Dysphagia completely disappeared. The patient had still some dyspnœa and pain. Though spontaneous remissions are natural, the authors feel at the end of 9 months of observation, that the disease has been arrested completely in the present case.

T. K. Mehta.

Indian Journal of Medical Sciences
(INCORPORATING THE MEDICAL BULLETIN)

VOLUME 5 NOVEMBER 1951 NUMBER 11

COPYRIGHT BY THE INDIAN JOURNAL OF MEDICAL SCIENCES

ORIGINAL ARTICLE

VALUE OF ELECTRO-ENCEPHALOGRAPHY IN CLINICAL MEDICINE

N. S. Vahia *

The paper is in response to a series of questions asked to the author after the establishment of an electro-encephalogram department at the K. E. M. Hospital, Bombay, in February last year.

Electro-encephalography is used by neuro-physiologists in the study of physio-chemical disturbances in the brain and also in the study of synaptic relationships between the cortex and subcortical tissue. This aspect of electro-encephalography will not be discussed here as the paper is limited to its value in clinical medicine only. It is used by clinicians as an aid in the study of neuro-psychiatric conditions, mainly for epilepsy and allied conditions, brain tumours, cerebral trauma, encephalopathies, cerebro-vascular conditions and impairment of special or general sensory or motor functions. A brief review of its value in these conditions is presented here.

EPILEPSY

It is uncommon to get an electro-encephalograph tracing during a clinical seizure but when such a tracing is obtained, it is of great value in the study of the conditions because each epileptiform attack has a distinct E. E. G. pattern. These paroxysmal E. E. G. seizures almost suddenly appear and disappear simultaneously in all the leads.

During minor epilepsy attacks, the E. E. G. shows distinct spike and wave patterns of the frequency of 1.5 to 3 per second. For practical purposes, such a paroxysmal outburst during a clinical seizure is diagnostic of idiopathic petit mal although it is possible to get this pattern in cases of cerebral tumour or trauma associated with epilepsy[9]. The E. E. G. has a prognostic value also, in the sense that slower the rhythm more grave the prognosis and vice versa.

---

*Hon. Psychiatrist, K. E. M. Hospital, Bombay.

During grand mal attacks, there might be first 4 to 7 per second activity lasting for a few seconds followed by very fast, about 30 per second, activity commonly associated with muscle artefacts, lasting as long as the convulsion and followed by low voltage slow activity,–this in turn being followed by normal alpha rhythm.

The grand mal pattern is of value in a diagnosis of epileptic disorder from other disorders but does not distinguish idiopathic grand mal from secondary grand mal.

The difference in diagnostic value between minor and major seizure patterns is that the former help in the diagnosis of the condition while the latter indicate the nature of symptom.[34]

The absence of E. E. G. change during seizure indicates that the attack is not epilepsy. If the normal features of an E. E. G. persist during a clinical attack, the attack is likely to be 'hysterical.'

From the point of view of clinical diagnosis it is the interseizure tracing that is of great importance.

The main interseizure peculiarities are the presence of rhythmic diffuse 1.5 to 3.5 per second activity, with or without foci of 3 per second activity in either cerebral hemisphere. Unusual prominence of fast activity about 30 per second is observed in interseizure tracing of epilepsy cases, particularly grand mal.

More characteristic are the wave and spike type outbursts lasting for less than a second much more common in the inter-seizure tracing of petit mal cases. A progressive increase of 1.5 to 3.5 per second activity of hyperventilation is quite common amongst all types of epileptic disorders.

Routine E. E. G. is of value in diagnosis in about 50 per cent of cases[10] and attempts are being made to increase its value by precipitating a latent epilepsy condition in the E. E. G. At present the following methods are mainly used to precipitate a paroxysm of cerebral dysrrhythmia in a case of epileptic disorder—hyperventilation, intravenous cardiazole[20] sleep, seconal[12] and photic stimulation[31]. Sometimes more than one method of stimulation is used. Without discussing the merits of each method, it might be broadly stated that by these methods, the chances of getting specifically diagnostic tracings have increased considerably.[3], [20]

Discussion of the value of E. E. G. in psychomotor attacks is purposely avoided here as the E. E. G. manifestation of these conditions are at present a matter of discussion.

BRAIN TUMOURS

An electro-encephalogram is mainly of value in connection with tumours from the point of view of localisation. Sometimes it provides the only evidence of a space occupying lesion. On the other hand it may sometimes be a confirmatory evidence of absence of a tumour[23].

ELECTRO-ENCEPHALOGRAPHY

TECHNIQUE OF TAKING BRAIN WAVES.

ELECTRODE APPLICATION:-

IN ALL 18 ELECTRODES ARE APPLIED AS A ROUTINE. TWO OF THEM ARE ATTACHED TO EAR LOBULES WHICH ACT AS NEUTRALS. THE REST SIXTEEN ARE APPLIED ON THE SCALP-(PREFERABLY SHAVED)-AS SHOWN IN THE DIAGRAMS.

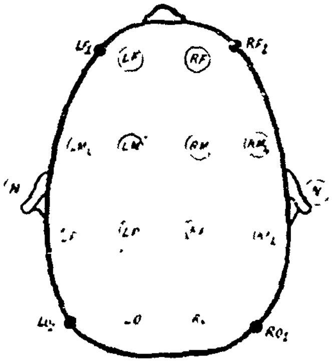


FIG.1. HEAD AS SEEN FROM ABOVE.

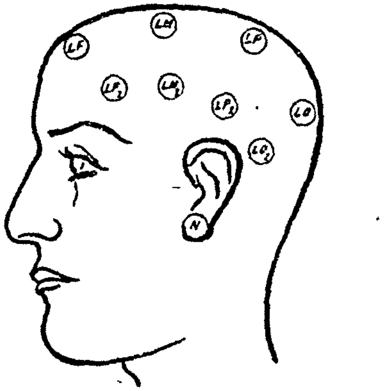


FIG.2. AS SEEN FROM LEFT SIDE.

ROUTINE SELECTION OF LEADS.

LEAD NO.1. LFM, LMP, LPO, RFM, RMP, RPO.
LEAD NO.2. LF_1M_1, LM_1P_1, LP_1O_1, RF_1M_1, RM_1P_1, RP_1O_1.
LEAD NO.3. LF_1F, LFRF, RFF_1, LM_1M, LMRM, RMM_1
LEAD NO.4. LP_1P, LPRP, RPP_1, LO_1O, LORO, ROO_1
LEAD NO.5. LF, LM, LP, LO, LM_1, LP_1.
LEAD NO.6. RF, RM, RP, RO, RM_1, RP_1.
LEAD NO.7. HYPERVENTILATION (CONNECTIONS AS LEAD NO.1)
LEAD NO.8. AFTER REST (CONNECTIONS AS LEAD NO.1)
LEAD NO.9. INTRAVENOUS 0.5 C.C CARDIOZOL (CONNECTIONS AS LEAD NO.1).

Fig. 1 & 2.—Electrode application in Electro-encephalography.

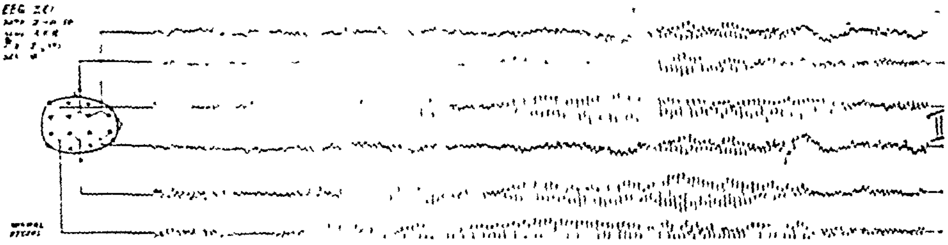


Fig 3 —E. E G.—normal record.

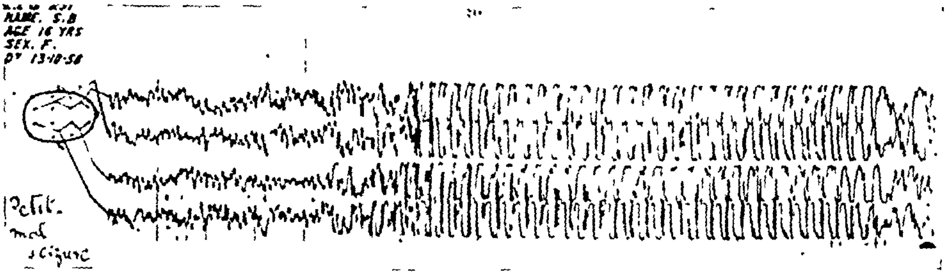


Fig. 4 —E E G —petit mal seizure.

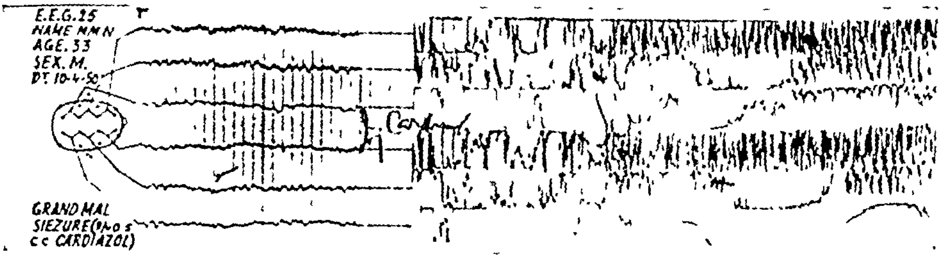


Fig 5.—E. E. G.—grand mal seizure.

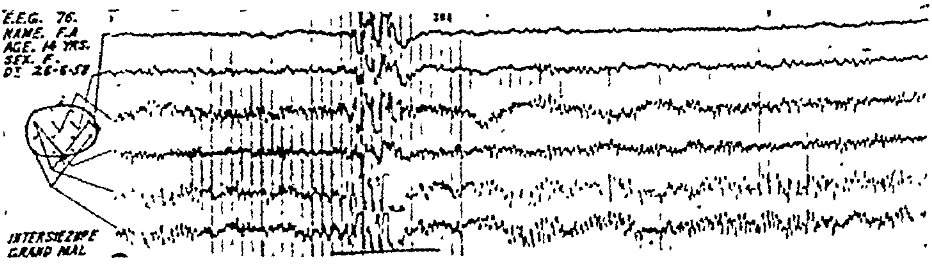


Fig. 6.—E. E. G —interseizure grand mal.

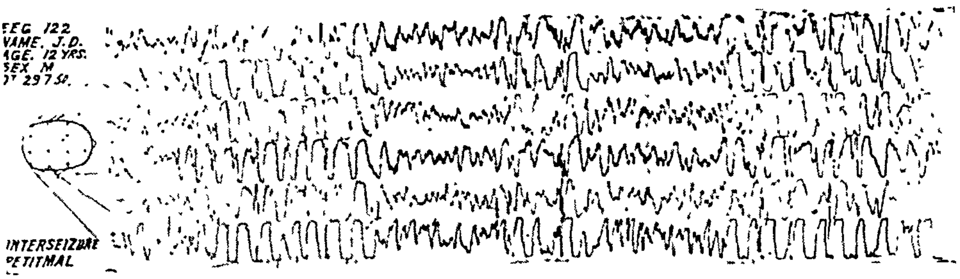


Fig. 7.—E. E. G.—interseizure petit mal.

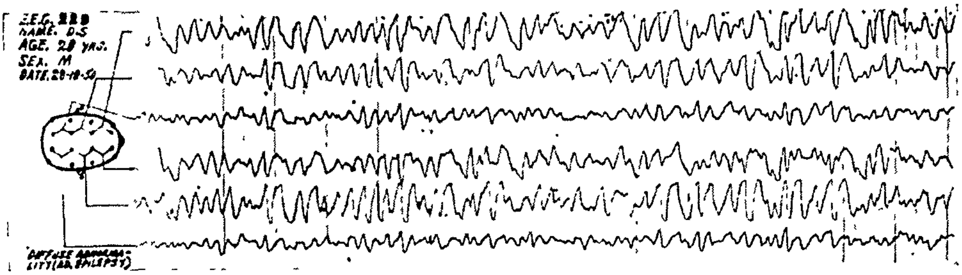


Fig. 8.—E. E. G.—diffuse abnormality.

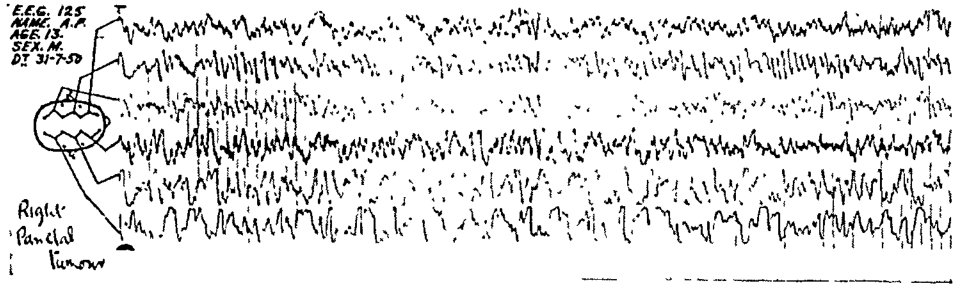


Fig. 9.—E. E. G.—right parietal tumour.

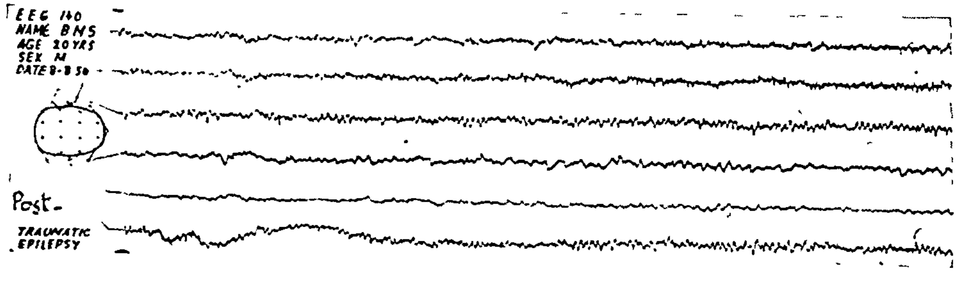


Fig. 10.—E. E. G.—post traumatic epilepsy.

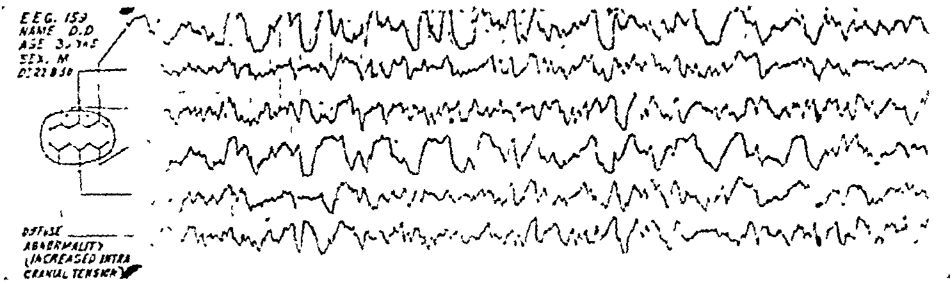


Fig. 11.—E. E. G.—diffuse abnormality (increased intra-cranial tension.)

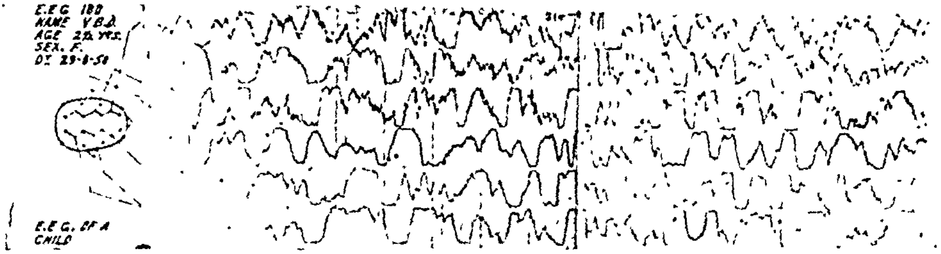


Fig 12.—E. E. G. of a child.

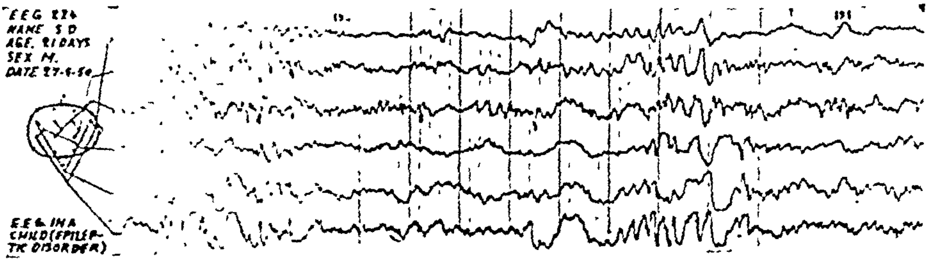


Fig. 13.—E. E. G.—epileptic disorder in a child.

The E. E. G. abnormality of importance for the location of a tumour is mainly local high voltage slow activity of 1 to 3 second activity. Focal 4 to 7 per second activity is also significant because it often indicates a deeply situated tumour. Presence of phase reversal is a very helpful sign but its absence does not exclude the possibility of a tumour. Existence of focal random spikes is of very great significance in the detection of a superficial lesion. Marked asymmetery on two sides is suggestive of the possibility of a tumour.

The word tumour signifies here any space occupying lesion although it must be noted that there is some difference in different space occupying lesions. Meningiomas show least abnormality in the E. E. G. and might even show a normal E. E. G. Gliomas show marked E. E. G. changes. Abscess looks like any other tumour except that the waves might be slower, irregular and focus might be more widespread. Secondary growths when single and granulomas like tuberculomas show no special E. E. G. peculiarities.[5]

From the point of view of localisation, a tumour on the outer side of the cerebral hemispheres is most readily and accurately localised although meningiomas are conspicuous exceptions. Subcortical tumours show localised 4 to 7 per second activity often associated with a more focal 1 to 3 per second activity. Some workers have used the relationship between 1 to 3 per second activity and 4 to 7 per second activity as a rough guide of the depth of a tumour. Parasagittal tumours are sometimes associated with normal tracings, probably because, they are often meningiomas and the brain involvement might be due to pressure and not due to damage to the cells[4]. Tumours at the base of the brain might show no abnormality at all or they might show bilateral 4 to 7 per second activity more marked in frontal regions. The abnormality might be asymmeterical if the tumour is away from the midline. Intrasellar pituitary tumours may show no abnormality in the E. E. G. Extrasellar pituitary tumours, if they are slowly growing, show no marked E. E. G. abnormality but rapidly growing pituitary tumours show bilateral 4 to 7 per second activity more marked in the fronto-parietal region, either symmetrical or asymmeterical, depending upon the situation of the tumour[25]. Tumours of the ventricles often show widespread symmeterical bilateral 4 to 7 second activity anteriorily. Tumours in the posterior cranial fossa are difficult to localise with E.E.G. partly because of their depth[39].

The E. E. G. is often complicated by the associated increase in the intracranial tension, which show diffuse abnormality in the E.E.G. and makes localisation of a tumour difficult, if not impossible[36]. One method of getting over this difficulty is to reduce the intracranial tension by injecting 50 c.c. of 50 per cent glucose and taking the E.E.G. tracing in 10 to 30 minutes after the injection.

This would show that the localisation of a tumour often becomes difficult on routine placement of electrodes, so now special electrodes are being devised to facilitate the study of different parts of the brain. Naso-pharyngeal electrodes[25] and tympanic electrodes[1,2] have been devised for the study of basal tumours. Special electrodes are devised to study the surface of the brain after opening the dura mater by operation[27] and some are devised for the study of E.E.G. changes in the depth of the brain tissue.[15]

Tumour tissue is electrically negative. It is the surrounding brain tissue that gives abnormal waves in the E.E.G. The degree of abnormality in an E.E.G. is proportional to the rate of growth, so that, more rapid the growth, greater the chances of getting an abnormal E.E.G. and vice versa.[31]

Absence of abnormality in the E. E. G. associated with definite clinical, roentgen, and other evidences indicate the possibility of benign nature of the tumour.[6]

HEAD INJURY

In severe head injuries, E.E.G. provides a measure of the severity of damage and might indicate unsuspected damage. It is also of help in recognition and localisation of intracranial hæmorrhage. In minor head injuries its routine use is of help in prognosis as it is a most sensitive indicator of head injury[14]

Immediate E.E.G. changes after head injury depend upon the severity of trauma and the condition of the patient. The late changes depend upon the residual and delayed changes in the brain. In severe cases, if a tracing is taken immediately, it shows either a 'flat' record or high voltage 1 to 3 per second activity all over the brain. This abnormality becomes less and less marked and alpha rhythm reappears till a state of equilibrium is re-established.

Gradual disappearance of slow waves and reappearance of 8-12 per second activity is rapid at first and slow later. The end result might be a normal record or a focus of abnormally slow or abnormally fast activity or generalised abnormality depending upon the residual damage. The severity of the abnormality is shown in the E.E.G. by the low frequency, high amplitude and irregularity of brain waves.

Scalp injuries do not show any marked E.E.G. abnormalities. Tears of the dura mater and penetrating brain injury show focal abnormality.

Subdural hæmatoma is indicated by generalised diminution in all electrical activity or 3 to 7 per second high voltage activity on the affected side[30] or more localised 1 to 3 per second activity[28, 30]. *Resolution* of record to normality is associated with clinical improvement[24] but if the E.E.G. is normal and there is clinical evidence of damage, it indicates complete destruction of certain cortical tissue and proper functioning of living cells indicating permanent nature of destruction. On the other hand, if the E.E.G. is abnormal and there is no clinical evidence of any damage, it indicates residual damages not clinically demonstrable, which might result in post traumatic epilepsy or post traumatic syndrome[37]

When records are made two years or more after head injury,the presence of generalised abnormality, if noticed, is not likely to be related to the head injury but focal abnormality is probably due to head injury.[13]

CEREBRO-VASCULAR CONDITION

In cases of intracranial hæmorrhage and infarction, the commonest abnormality is 1 to 3 per second focal activity somewhat similar to that in tumour. It is more localised and is associated with normal electrical activity over the rest of the brain, except when the patient is unconscious or when hæmorrhage is great causing increase in intracranial tension and giving rise to diffuse abnormality. The focal slow activity might persist but generally becomes slowly less marked as the healing process begins, so that if the infarct is subcortical, the E.E.G. might become quite normal. If there is persistent focal slow activity following a cerebro-vascular catastrophe in a young man after 2 weeks, it indicates unfavourable prognosis.[7]

PSYCHIATRY

At present E.E.G. enables a psychiatrist to know more about the organic disorders of the brain and helps to a certain extent in differentiating an organic psychosis from functional psychosis. It is also of value in differentiating hysterical convulsions from epilepsy and in distinguishing impairment of special senses like hysterical deafness or blindness from organic diseases involving this deafness or blindness.

Numerous E.E.G. studies have been made in cases of mental deficiency[21], hysteria and other psychoneurosis[16] and functional psychosis,[19], [32], but at present an E.E.G. is not of much value in diagnosis of these conditions.

The presence of a single focus of abnormally or abnormally slow activity suggests the presence of a cerebral lesion, either structural or functional. When it is associated with psychosis there is a possibility of an etiological relationship between the clinical condition and the E.E.G. findings.

An abnormal E.E.G. in an otherwise normal individual is an evidence of an inborn constitutional abnormality of the central nervous system which is not specific and which may manifest itself in the individual or in his children in the form of psychoneurosis, psychosis, psychopathic personality or an epileptic disorder[38].

At present the treatment of a behaviour problem child or a psychoneurotic adult is not influenced by an abnormal E.E.G. and there is no indication for withholding psychotherapy in a given patient because of the existence of some abnormal features in the E.E.G.[17]

ELECTRO-ENCEPHALOGRAM IN CHILDREN

At present the interpretation of E.E.G. of children presents special problems. The criteria established for adults do not hold good for children. Slow high voltage activity is quite common in young children and 4–7 per second activity which might be considered a significant abnormality in an adult is quite common in normal children. Alpha rhythm begins to appear in a child at about the age of 2 to 3 years and becomes a dominant rhythm about the age of 10 to 14 years. There is marked individual variation in E.E.G. records of normal children.[11]

Electrical activity of young brains is very susceptible to physical and chemical injury and children who respond to convulsions could only be considered to be cases of epilepsy after prolonged study.[8] Tumour localisation, on the other hand, does not particularly present great difficulties in children as compared to adults.[5]

Last year an electro-encephalogram department had been established at the K. E. M. Hospital and by now over 400 tracings have been taken. The electro-encephalograph is a six-channel Grass Instrument. As a routine, 16 electrodes are applied to the scalp and two electrodes are applied to the ears as 'neutral' electrodes. The 16 electrodes are placed in 4 rows, vertically, in the frontal, motor, parietal and occipital region, one row being near the midline on either cerebral hemisphere and another row about 2 inches away from the medial row. The method of electrode placement is shown in Figure 1. Both bipolar and monopolar technics of taking the tracings are being used as a routine procedure. Hyperventilation and intravenous cardiazole (5 mg.) are used to precipitate an E.E.G. seizure. The findings in the first 400 electro-encephalograms are stated in the adjoining charts.

As the number of cases of each type is comparatively small, no attempt is made to discuss the findings in detail, but a few significant features might be mentioned. Out of 153 cases with history of convulsive seizures the E.E.G. was normal in 40 cases. This does not mean that these 40 cases were not cases of grand mal. Another feature was that only 92 cases had shown diagnostic features of epilepsy. Without discussing details, it might be stated that "positive" tracing is of great significance but one normal tracing does not exclude the possibility of epilepsy. On the other hand, normal tracing in a definite case of epilepsy has some prognostic value.

TABLE 1.—*Analysis of E. E. G. Studies in Children.*

	No. of Cases.	Psycho motor pattern.	Petit mal pattern.	Grand mal pattern.	Combined grand petit mal	Diffuse very slow.	Slow activity.	Normal	Fast	Very Fast	Focal Fast	Focal slow.	Spikes.
Grand mal	63	..	2	34	2	9	5	11	..	1	..	..	1
Petit mal	16	..	5	..	3	..	..	8	..	..	..	..	..
Psychomotor	3	2	..	..	..	..	..	1	..	..	..	..	..
Mixed	3	..	1	2	..	..	..	..	..	..	..	..	..
Mixed petit mal and grand-mal	5	..	..	1	4	..	..	..	..	..	..	..	..
Recent head injury ..	1	..	..	..	..	..	..	..	..	..	..	..	1
Old head injury	..	..	..	..	..	..	..	..	..	..	..	..	..
Tumours	4	..	..	..	..	2	2	1	..	..	..	..	..
Encephalopathy	..	..	..	..	..	..	..	..	..	..	..	..	..
Cerebral-vascular disorders.	..	..	..	..	..	..	..	..	..	..	..	..	..
Mental defects	3	..	..	..	..	1	1	..	..	1	..	..	..
Mental deficiency with epilepsy	5	..	..	1	..	2	..	2	..	..	..	..	..
Psychosis	..	..	..	..	..	..	..	..	..	..	..	..	..
Psychoneurosis	..	..	..	..	..	..	..	..	..	..	..	..	..
Miscellaneous	5	..	1	2	..	..	3	..	..	..	..	..	..

TABLE 2.—*Analysis of E. E. G. Studies in Adults.*

	No. of Cases.	Petit mal.	Grand mal.	Combined grand petitmal.	Diffuse very slow.	Slow activity.	Normal.	Fast.	Very Fast.	Focal Fast.	Focal slow.	Spikes.
Grand mal	153	7	92	1	3	6	40	1	..	..	11	10
Petit mal	22	2	11	..	1	1	7	1	1	1	..	4
Mixed	12	1	2	..	..	..	7	1	..	1	..	2
Mixed Petit mal and Grandmal ..	8	2	2	6	..	..	1	..	..	..	..	..
Recent Head Injury	2	..	2	..	..	..	1	..	..	2	..	1
Old Head Injury	17	..	4	..	..	..	6	..	2	1	2	5
Tumours	44	..	8	..	2	3	16	..	..	..	13	7
Encephalopathy	..	..	..	..	..	..	..	..	..	..	..	..
Cerebral-vascular disorder	..	..	..	..	..	..	..	..	..	..	..	..
Mental defects	5	..	3	..	..	1	2	1	..	..	1	..
Mental deficiency with epilepsy ..	5	..	7	1	1	..	..	..	..	..	..	2
Psychosis	13	..	1	..	1	..	3	..	..	..	..	1
Psychoneurosis	3	..	..	..	..	..	2	..	..	..	..	1
Miscellaneous	25	..	5	..	..	2	15	..	3	..	2	2

So far as the tumours were concerned, the diagnosis of tumour had not been finally proved in all cases that were sent to the department with the clinical diagnosis of tumour, so that the significance of E.E.G. findings in these cases is not discussed here.

In conclusion it might be stated that electro-encephalography is one of the important technical developments in the study of neuropsychiatric disorders, but a clinician should be well conversant with its value and limitations, otherwise there is a possibility of misinterpretation of an electro-encephalographic record or report.

REFERENCES

1. Arellano, Z. A. P.: A Tympanic Lead, E. E. G. Clin. Neurophysiol. **1** : 112-113, 1949.
2. Arellano, Z. A. P. and Shwao, R. S.: Tympanic Leads and their Application to the MacLean Nasopharyngeal Leads for Basal Recording of the E. E. G., Amer. E. E. G. Soc. Proc. E. E. G. Clin. Neurophysiol. **1** : 524, 1949.
3. Brazier, M. A. B.: Electroencephalography. Progress in Neuro-Psychiatry, (Ed. Spigel) Grune-Stratton, N. York, **4** : 269-295. 1950.
4. Cobb, W. A.: The Electroencephalographic Localisation of Intracranial Neoplasms, J. Neuro & Neuro-psych. & Neuro-surgery. **7** : 96, 1944.
5. Cobb, W. A.: Intracranial Tumours. Electroencephalography. (Ed. Denis Hill) P. 296, MacDonald London, 1950.
6. Cobb, W. A.: Intracranial Tumours. Electroencephalography. (Ed. Denis Hill) P. 287, MacDonald, London, 1950.
7. Cohn, R.: Clinical Electrocardiography, P. 173, Mcgraw-Hill, Chicago, 1949
8. Cohn, R.: Clinical Electrocardiography, P. 603 Mcgraw-Hill, Chicago, 1949.

*9. Derbishire, A. J.: Experience with Localised Spikes and Slow Wave Patterns, Asstn. of E. E. G. Proc., E. E. G. Clin, Neuro-physiol **1** : 255, 1949.

10. Engel, G.L.: Clinical Application of E. E. G. Cincinnati Jour. of Med. **27** : 151-181, 1946.
11. Gibbs, A. E. and Gibbs, F. L.: Atlas of Electroencephalography, p. 110, Vol. I, 2nd Ed. Eddison-Wesley Press Inc., 1950.
12. Gibbs, A. E. and Gibbs, F. L.: Routine Seconal Sedation—A Major Aid to Clinical E. E. G. Am. E. E. G. Soc. Proc., E. E. G. Clin. Neurophysiol **1** : 245, 1949.
13. Gibbs, A. E. and Lennox, W. E.: E. E. G. & Epilepsy. Am. J. of Psych. **100** : 544-540, 1944.
14. Harris, H. I. and Wittson, C. L.: Value of E. E. G. in Prognosis of Minor Head Injury, War Medicine. **4** : 374-379, 1943.
15. Hayne, R. A. and Gibbs, F. A.: Electrical Activity of Subcortical Areas in Epilepsy, Am. E. E. G. Soc. Proc., E. E. G. Clin. Neuro-physiol. **1** : 47, 1949.
16. Heppenstall, M. E., Hill D. and Slater, E.: E. E. G. in Prognosis of War Neurosis, Brain, **68** : 17-22, 1945.
17. Hill, D.: Electroencephalography., p. 363, MacDonald, London 1950.
18. Hoch, P. H.: Clin. & Biological Relation Between Schizophrenia and Epilepsy, Am. Jour. of Psychiatry. **99** : 507-512, 1943.
19. Jasper, H. H., Kershman, J. and Elvidge, A.: E. E. G. Studies of Injuries to Head. Arch, Neurol. & Psychiat. **44** : 328-250, 1950.
20. Kaufmann, I. C. and Watson, C. W.: A Brief Review of Methods Used to

Elicit or Accentuate Abnormalities in E. E. G., E. E. G. Clin. Neurophysiol. **1** : 237, 1949.

21. Kaufmann, I. C. Marshall, C. and Walker, A. E. : Activated Electroencephalography, Arch. Neurol. & Psychiat. **58** : 533-549, 1947.
22. Kreezer, G. : Electrical Potential of the Brain in Certain Type of Mental Deficiency, Arch. Neurol & Psychiat. **36** : 1206-1213, 1936.
23. Kershman, J. and Conde, A. : E. E. G. in Diff. Diagnosis of Supratentorial Tumours, Arch. Neurol & Psychiat. **62** : 255-268, 1949.
24. Laufer, M. W. and Perkins, R. F. : Study of E. E. G. in 209 Cases of Head Injuries at an Army Neurological and Neurosurgical Centre, Nerv. Proc. Neuropsychiat. Conf. Sixth Service Command, pp. 118-124, 1945.
25. Lennox N. and Brody, B. S. : Paroxysmal Slow Waves in E. E. G. of Patients with Epilepsy and Sub-cortical Lesion, J. of Nerv. & Ment. Diseases. **104** : 237-248, 1946.
26. MacLean, P. D. : A New Nasopharyngeal Lead, E. E. G. and Clin. & Neuro-Physiol. **1** : 110, 1949.
27. Marshall, C. : Corticographic Electrodes, E. E. G. and Clin. & Neuro-Physiol. **1** : 110, 1949.
28. Rogers, L. : E. E. G. in Traumatic Intracranial Hæmorrhage, B. M. J. **1** : 510-511, 1941.
29. Sjaardema, H. & Glaser, M. A. ; E. E. G. Diagnosis of Subdural Hæmorrhage, Ann. Surg. **116** : 452-460, 1942.
30. Sullivan, J. Abbott, J. A. : E. E. G. in Subdural Hæmatoma, E. E. G. Clin. & Neuro-Physiol. **1** : 517, 1949.
31. Ulett, G. : Electro-encephalogram of Dogs with Experimental Space Occupying Intracranial Lesion, Arch. Neuro. and Psychiat. **54** : 141-149, 1945.
32. Walter, V. J. , and W. G. : The Central Effects of Rhythmic Sensory Stimulation, E. E. G. J. of Clin. Neuro-physiol. **1** : 57, 1949.
33. Walter, W . G., *et al* : E. E. G. in Mental Disorders. J. Ment. Sc. **88** : 110-121, 1942.
34. Walter, W. G., *et al* : Analysis of Electrical Response of Human Cortex to Photic Stimulation, Nature, **158** : 540,-541, 1946.
35. Walter, W. G. *et al* : Epilepsy-Electroencephalography, p. 234. MacDonald, 1950. London.
36. Williams, D. : The Abnormal Cortical Potentials Associated with Increased Intra-cranial Tension, Brain, **62** : 321-334, 1939.
37. Williams, D. : E. E. G. in Chronic Post-traumatic States, J. of Neuro. & Psych. **4** : 131-146, 1941.
38. Williams, D. : Significance of an Abnormal E. E. G. J. of Neuro. & Psych. **4** : 257, 268, 1941.
39. Williams, D. J. and Gibbs, F. A. : Localisation of Intra-cranial Lesions by E. E. G. New England J. Med. **218** : 998-1002, 1938.
40. Williams, D. and Denny-Brown, D. : Cerebral Electrical Changes in Experimental Concussion, Brain, **64** : 223, 238, 1941.

ORIGINAL ARTICLE

CORONARY HEART DISEASE

A review of 200 cases

R. P. Malhotra *

This is a study of 200 cases of coronary heart disease that I have seen within the last four years at Amritsar. Vakil[15] (1949) from Bombay gave a review of 250 cases of this disease from amongst his total cardiac population of 1860 cases, and it may interest you to compare his observations with some of my findings in this province.

CLINICAL MATERIAL

This clinical material represents a fair estimate of both hospital and private class of patients. The list in Table 1 includes cases seen at the cardiology clinic, in the general and the private wards of the professor of medicine, and private cases seen outside.

TABLE 1. *Distribution of Cases of Coronary Disease Seen in Private Practice, Cardiology Clinic, and General Wards of the V. J. Hospital, Amritsar.*

Total number of cases.	Private cases		Cardiology clinic cases		General ward cases.	
	No.	Percentage.	No.	Percentage.	No.	Percentage.
200	81	40.5	73	36.5	46	23

Evidently the number of patients seen in private practice tops the list. Comparing these figures with those of the rheumatic group shown in Table 2, it shows that the number of hospital class of patients is nearly 4 times the number seen in private practice.

TABLE 2. *Comparative Distribution of Cases of Rheumatic Heart Disease with Coronary Disease.*

Disease	No. of cases	Private		Clinic		General wards.	
		No.	Percentage	No.	Percentage	No.	Percentage
Coronary Disease ..	200	81	40.5	73	36.5	46	23
Rheumatic Heart Disease ..	140	22	15.7	35	25	83	59.3

GENERAL INCIDENCE

Table 3 represents the general incidence of coronary heart disease as compared to other cardiac diseases. From October '46 to August '50 806 cases were examined for heart disease. For purposes of general incidence and to have a correct estimate, it was decided to combine,

---

*From the Cardiology Clinic, V. J. Hospital Amritsar

TABLE 3. *Incidence of Various Heart Diseases Reported by Some Workers (India and Ceylon).*

Name	Vakil (Bombay) (1949.) 1860 cases.		Sanjivi (Madras) (1946). 616 cases.		Devi Chand (Lahore) (1946). 112 cases.		Guniwerdene (Ceylon) (1935) 455 cases.		Authors (Amritsar) (1950-series). Total 692	
Type of diseases.	No.	%	No.	%	No.	%	No.	%	No.	%
1. Congenital	19	1	..	2.3	3	2.68	..	1	58	8.4
2. Rheumatic heart disease	461	24.8	..	46.8	31	27.68	..	20	140	20.2
3. Hypertension coronary group	617	33.2	..	29.5	28	25	..	15.5	333 (Hypertension 176 Coronary disease 162)	48.8
4. Cardiovascular syphilis	240	12.9	..	6.5	9	8	..	10	15	2.2
5. Cor. Pulmonale	186	10	..	..	6	5.4	..	..	38	5.5
6. Miscellaneous	337	18.1	..	..	..	..	..	..	103	14.9
7. Cardiac Neurosis	..		..	..	..	..	..		114	14.1
									Total ..806	

hypertension and coronary disease together and designate it as 'Hypertension-Coronary group'. These 200 cases were clinically of the coronary type with dominant features of this disease. Many of them had associated hypertension, while others who exhibited normal or subnormal levels of blood pressures at the time they presented, might have had hypertension before. Keeping in view the great likelihood of these entities overlapping each other, it was thought advisable to consider them together in a general assessment of arterial disease of the heart. On considering all the heart diseases together this group apparently takes the lead. You may compare these figures with those of Vakil[15] (1949) with those of Devi Chand[2] (1946) and those of Sanjivi[11] (1946) from Madras. In Vakil's series also, this group is the leading cause of heart disease. Sanjivi in his analysis of 616 cases reports an incidence of coronary disease as 13 per cent and of hypertension as 16.5 per cent making a total of 29.5 per cent. In his series rheumatic heart disease seems to be the leading cardiac malady, but his report represents cases from the general wards only, there being no mention of his private cases. Devi Chand in his analysis of 112 cases reports the incidence of coronary hypertension group as 25 per cent. In his series also rheumatic heart disease tops the list, which however includes only 13 private cases. Devi Chand however records 8 cases suffering from chronic myocardial disease, by which, I presume he means the degenerative group of heart disease. If these cases are included in coronary hypertension group his figures will show an incidence of 32.14 per cent. Wig (1946) in a discussion, before the association 4 years ago, on the incidence of heart disease, strongly emphasised that if one took into account the private class of patients also, hypertension became the leading group. After having observed and kept personal records of all the heart cases seen in the hospital as well as in private practice, I entirely agree with him that for a proper analysis of the cardiac disease the private class of patients must not be excluded. However, it is beyond dispute that if one were to consider the hospital class of patients only, the rheumatic group would certainly lead the list. Guniwerdene from Ceylon in his analysis of 455 cases belonging to the hospital class, has reported an incidence of 15.5 per cent as compared to 33 per cent of Vakil and 48.8 per cent of my cases.

INCREASE IN INCIDENCE

It is difficult to prove with statistical accuracy that the disease is on the increase. Every year I am seeing more cases as compared to the year before. A physician with a bias towards cardiology is likely to see more and more heart cases every year for obvious reasons. The best judges to give an opinion on this controversial issue are the general physicians. Some of them admit that they see more cases of this disease than they used to see ten or fifteen years ago. It was in 1912 that coronary thrombosis was first described by Herrick in America, while in England it was brought to the notice of the profession by McNee[11] in 1925. Improved diagnostic acumen in the medical world leading to a better and early diagnosis is one of the reasons given for the increase in incidence, but I may quote Cassidy[1] (1946) here who in his Harvein oration in 1946 said, "Even so I have the impression that coronary thrombosis is far more common than it was."

In the year 1926, 1880 cases died of coronary disease in the U. K. whereas by 1939 this number had reached an astounding figure of 19,496 (Cassidy[1] 1946). While comparing the small series given by Osler, Mackenzie, and Douglas Powell, Cassidy further says, "Contrast these figures with those of the modern cardiologist who counts his coronary cases by thousands rather than hundreds and remember— that there was but one James Mackenzie and one William Osler, whereas the modern cardiologist's name is legion: Surely Osler, Mackenzie, and Douglas Powell were at least as competent to diagnose angina pectoris as are the physicians of this generation."

To give a convincing statistical proof that the disease is on the increase is difficult; but to explain as to why it has increased is still more baffling.

AGE

The age distribution of the disease is given in Table 4.

TABLE 4. *Distribution of Coronary Disease According to Age Periods.*

Total No.	Below 20		20–29		30–39		40–49		50–59		60–69		70–79		80–89	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
200	–	–	4	2	12	6	50	25	81	40.5	40	20	13	6.5	–	–

No case was seen below the age of 20 and over the age of 80. It will be seen that the peak period is reached in the age group 50—60. Next groups in order of frequency are 40—50 and then 60—70. Levine from America, Parkinson and Bedford from England and Cassidy again from England have reported the peak incidence in the age group 60—70. Freidbergh[4] from America reported the maximum incidence between 50—60. In our own country Vakil reports the maximum incidence in the age group 40—50, a decade lower than my figures and those given by Western workers. In any case about 85 per cent of the cases occur between the ages of 40—70. I would, however, draw your attention to the age group below 40. This includes 16 (8 per cent) of my cases. 4 cases belonged to the age group below 30. The incidence of coronary disease in the young has been emphasised in recent years by many workers, particularly, amongst

American troops during the war (Yater *et al*[18] 1948). An extensive account of coronary disease between the ages of 18—39 was given by Yater and others (1948) reporting 866 cases with 450 necropsy reports. Coronary disease in the young, *i.e.*, below the age of 40 is not uncommon. In my 200 cases their number was 16, (8 per cent). Vakil's figures are still higher. He reports 41 cases, 16 per cent of his total of 250 patients. Heiling (1943) has reported a case of coronary disease in a young man of 19, and Dhanda (1946) mentioned 4 years ago before this Association about a young lad of 18 with coronary thrombosis. If the clinical picture of a patient is in favour, age should be no bar in making a diagnosis of coronary disease. One should be very careful in dismissing this diagnosis particularly in those young people who have a positive history of arterial disease or diabetes in the family. Recently, I saw a young man of 33 who complained of left inframammary pain, fatigue, insomnia and some of the other features of DaCosta's syndrome. He had a family history of coronary disease in both the parents and in one elder brother. When I took his cardiogram I was surprised to find a bundle-branch block.

SEX

Literature from Western countries gives a ratio of males to females as varying between 2 : 1 to 6 : 1. A report from the Mayo Clinic (Parke *et al*[12]-1946) quotes it as 4.3 to 1. In India the gap seems to be wider. Vakil has analysed it as 8.6 to 1, while in my series there were 24 females constituting a ratio of 7.3 to 1. Levy and Boas[10] (1936) have mentioned that coronary disease occurs mostly in those females who are either diabetic or hypertensive. This was true of my patients also, so far as association of hypertension with coronary disease is concerned. Of the 200 cases, association of hypertension was noted in 36 per cent of the male cases, while in females the figure was 47 per cent. The incidence of associated diabetes in these cases showed no difference so far as sex was concerned.

Why the female sex enjoys a comparatve immunity towards coronary disease is not clearly understood. Dock[3] (1946) carried out investigations on the coronary arteries of newly-born dead babies and found that the arterial intima of the coronary vessels in the males was much thicker than in the females. His views are that the male sex is anatomically predisposed to the disease.

SOCIAL AND ECONOMIC STATUS

For purposes of classification the patients were divided into three main classes :—

Upper class :—This included patients who came mostly from the upper and professional classes like business magnates, lawyers, engineers, doctors, high salaried government officials, ministers, judges, etc..

Middle class :—Some of the professions with income levels between Rs. 100-500 were included in this class, e.g., clerks, school teachers, petty shopkeepers, etc.

Lower class :—People with income levels below Rs. 100, e.g., skilled and unskilled workers, farmers, etc. Their distribution is given in Table 5.

TABLE 5. (*Classification of Cases According to Economic Status.*)

No. of cases.	Upper Class.		Middle Class.		Lower Class.	
	No.	%	No.	%	No.	%
200	62	31	108	54	30	15

It is commonly believed that the incidence of coronary disease is more common in professional and upper classes. Table 6 shows figures published by Hedley[6] in 1939 and they are interesting.

TABLE 6. *Distribution of Deaths from Coronary Occlusion Per* 100,000 *in Different Occupations* (*Hedley* 1939).

Occupation.	Deaths from coronary occlusion per 100,000	Occupation.	Deaths from coronary occlusion per 100,000
Professional	154	Clerks and salesmen	128
Managers and officials	140	Skilled and unskilled workers.	107

The maximum number of cases came from the upper and the middle classes while only 15 per cent belonged to the lower classes. 31 per cent of patients were from the upper class. Compare these figures with rheumatic heart disease. Table 7 shows cases of rheumatic heart disease seen in one year.

TABLE 7. *Distribution of Rheumatic Cases in One Year According to Economic State.*

No. of cases.	Upper class.		Middle class.		Lower class.	
	No.	%	No.	%	No	%
72	5	6.9	35	48.6	32	44.4

Out of 72 cases of rheumatic heart disease only 5 came from the upper class, whereas 32 represented the lower class. The upper class figures 6.9 per cent only in the rheumatic group whereas in the coronary group they formed 31 per cent.

URBAN VERSUS RURAL

Of the 200 cases, 112 belonged to Amritsar town while 38 came from the mofussil areas. In the latter group 27 cases were from small villages, the rest being from other towns of the province. Statistically, one cannot prove that the disease is uncommon in the rural areas. One may further add that coronary disease as compared to rheumatic heart disease carries much heavier mortality and only such patients are likely to visit the hospitals in the towns who linger on with congestive heart failure, or who are severely disabled with angina pectoris. Rural patients with a brief illness of coronary episode are not likely to seek medical advice in the cities where they could be spotted easily. Last year in the rheumatic group, 33 per cent patients came from the rural areas while in the coronary group they figured 13.5 per cent.

FAMILY HISTORY

Family history was known to 138 patients and the incidence of a positive history was obtained in exactly 50 per cent of them. While recording the family history one should get into the details of the cause of death in the members of the family. Such a simple question as to whether there is any heart disease in the family, is not enough. To a lay mind, heart disease or heart failure is generally associated with the idea of sudden death. A person may have died of slow insidious congestive heart failure. Some patients mention asthma as the cause of death and it is only on getting into details that one finds that the so called asthma was of short duration only and in reality it was cardiac asthma. History of angina pectoris or coronary thrombosis need not always be present. Other manifestations of arterial disease and cerebral vascular accidents should also be borne in mind. While going through the histories of my cases at Amritsar I have been more than surprised to find that in several families not only a positive history of vascular disease was present but even the clinical pattern was also the same. Several members would be struck by either a cerebral stroke or a coronary episode. I am convinced that the family history plays a very dominant role in this disease. Whether or not it is due to any vascular inferiority due to hereditary factors is difficult to prove, but experiments on the same lines as Dock carried out may throw some light. A careful examination of the coronary arteries of the children coming from a stock suspected of dying of accidents or other diseases may reveal some valuable information which may provide food for thought regarding preventive measures.

DIET

I started collecting the records of my cases just after the last war when the times were abnormal but worse came from the partition upheaval in the province disturbing the economic condition of so many people. Many people who were used to a much better standard of living now found themselves in different circumstances. A history of consistency in the standard of diet could not be obtained. At any rate it may be of some interest to mention that 148 patients were non-vegetarians while 52 were vegetarians.

ALCOHOL AND TOBACCO

History of taking alcohol in moderation or in excess was positive in 89 patients. People taking an occasional drink were excluded. Regarding tobacco most of the authorities agree as to there being no proof of its predisposing to this disease—at least no definite proof can be given. One reason for condemning it is its definite association with another arterial disease—thrombo-angitis obliterans. Some people have described 'Tobacco Angina' while others have completely denied it. In heavy smokers with angina I have gone into this fact without coming across any patient who exhibited this condition. Out of my 200 cases, history of tobacco smoking or chewing was present in 60 cases, but here it may be of some significance to mention that 81 of them were Sikhs who do not smoke on religious grounds. Unless one knows the exact incidence of smoking in the general population and compares it in non-cardiac diseases also, it is difficult to incriminate it as an important ætiological factor.

BODY-BUILD

Patients were classified into three groups—obese, average, and thin. They are shown in Table 8.

TABLE 8. *Distribution of Cases According to Body Build.*

No of cases	Obese		Average build.		Thin.	
	No.	Percentage.	No.	Percentage	No.	Percentage.
200	74	37	94	47	32	16

It is apparent that the incidence is less in thin people. Obesity has been blamed in hypertension and diabetes, both of which are closely related to coronary disease. It is significant that only 16 per cent of patients were of thin build.

ASSOCIATED DISEASES

Table 9 shows the relative association of hypertension, diabetes, syphilis, and rheumatic heart disease with coronary disease.

TABLE 9. *Association of Hypertension, Diabetes, Syphilis, and Rheumatic Heart Disease With Coronary Disease.*

No. of cases.	Hypertension		Diabetes		Syphilis.		Rheumatic Heart Disease.	
	No.	%	No.	%	No.	%	No.	%
200	83	41.5	38	19	18	9	1	0.5

In voluminous literature on coronary disease the association of hypertension with this disease has been emphasised giving a greatly varying picture. Associated incidence of hypertension with this disease has been reported as 25 per cent by some, while others have given a high figure of 75-80 per cent. In my series hypertension past or present was evident in 41.5 per cent of cases. Diabetes was present in 19 per cent of cases, syphilis in 9 per cent of them. There was a solitary case of rheumatic heart disease who had coronary heart disease in addition.

CLINICAL FEATURES

You are fully familiar with the usual symptoms of this disease. My object is to draw your attention to only a few significant facts. Out of 200 cases, 99 had evidence of myocardial infarction as the main feature either on past history or on present clinical grounds, or on electro-cardiographic evidence. Angina of effort as the only complaint without any history or evidence of infarction was present in 77 cases, whereas of 99 cases of infarction, 47 had angina as associated feature. It will not be possible to discuss all the clinical features in detail. I would discuss and emphasise only a few of them.

TABLE 10. *Showing Some of the Main Clinical Features.*

Angina preceding infarction	10
Infarction preceding angina	33
Angina at rest	13
Premonitory Angina	20
Symptoms of congestive heart failure at the onset of infarction	40
Insidious congestive heart failure without any angina or infarction	18
Infarction as the first symptom	88
Location of pain in atypical areas	10
Sense of impending dissolution	28
Sudden dyspnœa as the main symptom	38
Shock at the onset of infarction	49
Nausea and vomiting at the onset	49
Acute left heart failure	49
Simulating other diseases	11

Premonitory Angina :—Out of 99 cases of infarction, 22 gave a history of what is called premonitary angina. Various reporters have given the incidence of premonitory cardiac pain in 10-50 per cent of their cases. Patterson[13] (1939) regards this prodromal angina as due to initial capillary hæmorrhage and hæmatoma formation in the coronary arteries. This prodromal pain is a warning and may be present a few days preceding the proper attack. It has its implications in the treatment and such patients should be treated as if a full-fledged attack had already taken place. It is pertinent to presume that such patients may be given anti-coagulants as a preventive measure. This premonitory pain is like angina pectoris in other characters except that the attacks are more frequent, last longer, and come on at rest also. Such a patient is a potential candiate for infarction and would better be treated as any other case of myocardial infarction.

Acute coronary failure:—This manifestation of coronary disease in its clinical aspects holds an intermediate position between myocardial infarction and angina pectoris. Such a patient may have an attack of pain for half an hour or so, coming on at rest or exertion and may be associated with a mild degree of shock. There may be no permanent electro-cardiographic changes. Such patients should again be regarded as potential candidates for a major coronary episode and treated as such despite negative electrocardiographic findings. Of my cases, 5 presented this clinical picture.

Sudden dyspnœa as the main symptom:—In 38 cases of infarction no history of pain was present, instead, they gave a history of dyspnœa starting suddenly without any previous history of angina or exertional dyspnœa. Pain may sometimes be so minimal, or dominated completely by dyspnœa, that it may have been forgotten by the patient and is reminded by a leading question. Some of these patients get wrongly diagnosed as bronchial asthma. In any middle age person dyspnœa starting suddenly without any previous history of bronchial asthma may wisely be considered cardiac unless proved otherwise.

Insidious congestive heart failure:—These are patients who start their coronary disease neither as infarction nor as angina nor as acute left heart failure, but slip into a state of slow, insidious congestive heart failure. When I was a student some patients of this description go labelled as chronic myocarditis. This diagnosis seems to have disappeared from the wards now. With proper electrocardiographic investigations such patients are usually found to be suffering from coronary disease. After complete investigations very few cases are left with the diagnosis of congestive heart failure of obscure ætiology. Of my cases, 18 presented as slow insidious congestive heart failure.

COMPLICATIONS

Some of the important complications are shown in Table 11.

TABLE 11. *Complications.*

Thrombo-embolic phenomena	2
Congestive heart failure	92
Arrhythmias	27
Perforation of the inter-ventricular septum	1
Super-added neurosis	13
Peri-arthritis of the shoulder	5
Ventricular aneurysm	1

Forty-six percent of patients sooner or later developed congestive heart failure which may be regarded as an important complication in as much as it accounted for nearly half the deaths. The incidence of thrombo-embolic phenomena appeared to be low in contrast to the reports of some of the Western workers. In myocardial infarction the reported incidence of embolism has varied from 11 per cent to 60 per cent. Vakil has reported this complication in only five of his 250 cases. Personally, I believe that the incidence of thrombo-embolic phenomenon is low for three reasons. First comes the great handicap in lack of autopsy material from our cases here. Out of 33 deaths an autopsy could be performed only in one case. Secondly, many cases of infarction are not subjected to routine rœntgenographic examination for it is obvious that they should be disturbed as little as possible. Routine portable rœntgenography in such cases is a luxury not afforded at present. nor do I believe that portable pictures are likely to reveal much in small pulmonary infarctions. The third reason for seeing fewer thrombo-embolic phenomena in this disease is that private cases do not seek hospitalization and day to day observation of this complication is not possible in the patients' own homes. For several years I have been quite conscious of the high figures of pulmonary embolism reported by Western workers, both in medical as well as in surgical cases, and I have been on the lookout for this complication. Our low figures may be due to lack of routine rœntgen investigations and the rare availability of autopsy material. Regarding other complications, it would suffice to add that super-added neurosis is not uncommon in these patients but one's experience and clinical judgment eliminates the difficulty in differentiating between the psychic and the somatic components of a patient's illness.

FOLLOW-UP AND MORTALITY

Out of 200 cases, 103 could be followed up completely while 24 were partially followed up. Out of 103 cases followed up-to-date, 33 are dead. It is not possible to draw definite conclusions regarding the prognosis in a follow-up of four years only. At present we depend for our judgment regarding prognosis on the observation and follow up of Western workers. It is high time that we kept a proper follow-up of our cases and came to some conclusions some years later in our own clinical material. My follow-up and study in these cases dates back to October 1946. If I am given an opportunity to address you on this subject some years later I may be in a better position to present a more reasonable account of survival period and prognosis in our own patients. Yodh stressed the importance of proper records and follow up of such cases and I believe many other physicians in the country must be following his advice.

Bland and White[16] in 1941 reported a follow-up of over ten years in a series of 200 cases of myocardial infarction. 25 per cent of their cases lived over ten years after the first attack. In another report in 1943, White, Bland and Miskall[17] gave the average life after the first symptom of coronary disease as 7.9 years, the duration of observation being 23 years. The present trend of opinion is to take a more optimistic attitude towards the disease. With early diagnosis and better follow-up the survival period has been reported longer and longer in recent years. It may be of some interest to mention the coronary life span of three of the most distinguished medical men who have left a great mark in the history of cardiology, *i.e.* John Hunter (1773-93) lived for 20 years, Sir James Mackenzie (1907-25) for 18 years and Sir Thomas Lewis (1927-45) for 18 years.

The survival period of those cases that have been followed up in the present series is shown in the Table 12.

TABLE. 12. *Survival Period.*

	Below 1 month	1–2 months	3–6 months.	6–12 months	1–2 years	2–4 years	4–6 years
After onset of infarction ..	16	..	3	3	1	2	1
After onset of angina ..	2	..	3	1	2	2	2
After onset of congestive heart failure..	10	1	5	4	3	1	..

Out of 99 cases of infarction that I have seen within the last 4 years, 26 cases are known to be dead. Of these, 16 cases died within a month whereas 22 (*i.e.*, 84 per cent) died within a year. In cases of angina pectoris the survival period was evenly distributed. Out of 92 cases who developed congestive heart failure 24 died, of which 20 (*i.e.*, 83 per cent) were dead within a year. From Table 12 one can judge that the first month after infarction is a dangerous period and if a patient survives the first month, one can look forward with some optimism unless a case goes into congestive heart failure. Once congestive heart failure sets in after infarction in a patient, there are very few chances of his survival for more than a year.

Mortality according to age period :—Table 13 represents the mortality rate in terms of age periods.

It shows that the mortality rate is highest either in the very young or in the age group 60—70. This has been the observation of some of the other workers also. Sex made no difference in the mortality rate of my cases.

ELECTROCARDIOGRAPHIC STUDY

Electrocardiographic studies could not be undertaken in 18 cases for some reason or another. The analysis of 182 graphs is shown in

TABLE 13. *Mortality Rate in Terms of Age Periods.*

No. of cases.		20—29			30—39			40—49			50—59			60—69			70—79		
No.	deaths	No.	deaths	%	No.	deaths	%	No.	deaths	%	No.	deaths	%	No.	deaths	%	No.	deaths	%
200	33	4	3	75	12	1	8.3	50	5	10	81	10	12.3	40	11	27.5	13	3	23.1

Table 14, which is an electrocardiographic analysis of various patterns taken in 182 cases.

TABLE 14. *Electrocardiographic Analysis of Various Patterns.*

No. of cases where the E. C. G. was taken	182
Normal graphs	24
Abnormal graphs	158
Normal E. C. G. in cases of angina pectoris (out of 77)	24
Anterior myocardiac infarction	31
Posterior myocardiac infarction	23
Mixed infarction	5
Bundle branch block	18
Miscellaneous	87

In 31 per cent of the cases of angina pectoris the E. C. G. pattern was quite normal. Previously, we had an old German Electrocardiograph which was difficult to operate and routine precordial exploration could not be done in all the six places. For the last one year we are working with a modern cardioscribe and routine 12 lead electrocardiograms are being taken, i.e., three standard limb leads, three unipolar limb leads and six unipolar chest leads. Within a year I have been greatly impressed by the utility of precordial exploration over all the six places, as a contributing factor towards the diagnosis of coronary disease. In several cases, I can show you a number of graphs which show either no change, or only a suspicious alteration in the standard limb leads, but precordial exploration reveals the true picture. If the clinical picture is suspicious but the standard limb leads and one chest lead are normal it is unwise to dismiss the diagnosis without complete precordial exploration.

SUMMARY AND CONCLUSIONS

A study of 200 cases of coronary disease with a follow up of four years is presented.

1. Coronary disease along with hypertension, i.e., 'Arteriosclerotic Heart Disease' is the leading cause of heart disease in this province.

2. For a proper assessment of the incidence of coronary disease it is necessary to include private patients also, as in hospital practice of the general wards rheumatic heart disease tops the list.

3. Coronary disease is not uncommon in the younger age group and carries a heavy mortality in the very young.

4. A few clinical features like sudden dyspnœa, premonitory angina, acute coronary failure, slow insidious heart failure are also discussed.

5. The incidence of thrombo-embolic phenomena is mentioned and reasons given for its low incidence in our cases.

6. Importance of electrocardiographic study with particular reference to complete precordial exploration is stressed.

ACKNOWLEDGMENT

I am very thankful to Dr. K. L. Wig for giving me permission to publish these cases and Dr. P. N. Chhuttani for helpful suggestions. I will be, however failing in my duty if I do not express my gratitude to my house physician Dr. Nasib Singh Pathania without whose help it would have been very difficult to go through such a large number of histories.

REFERENCES

1. Cassidy, M.: "Coronary Disease" Harvein Oration, Lancet, **2** : 587-590, 1946.
2. Devi Chand: "Heart Disease in the Punjab," Proceedings of the Association of Physicians, India, 1946.
3. Dock, W.: Predilection of Atherosclerosis for Coronary Arteries, J. A. M. A. **131** : 875-878, 1946.
4. Freidbergh: Diseases of the Heart, W. A. Saunders, Philadelphia, 1950.
5. Garvin, C. F.: Mural Thrombi in Heart as Source of Emboli, Am. J. M. Sc., **201** : 412-415, 1941.
6. Hedley, O. F.: Analysis of 5116 Deaths Reported as Due to Coronary Occlusion in Philadelphia, Public Health Report, Washington, **54** : 972-1012, 1939.
7. Heilig, R.: Angina Pectoris in Past and Present with Special Reference to Treatment, Indian Physician **2** : 205-224, 1943.
8. Hellerstein, H. K. and Martin, J. W.: Incidence of Thrombo-Embolic Lesions Accompanying Myocardial Infarction, Am. Heart J. **33** : 443-452, 1947.
9. Levine, S. A.: Coronary Thrombosis, Williams and Wilkins, Baltimore, 1929.
10. Levy, H., and Boas, E. P.: Coronary Artery Disease in Women, J. A. M. A. **107** : 97-102, 1936.
11. McNee, L. W., Quart. J. Med. **19** : 44, 1926.
12. Parker, R. L., Dry, T. J. Willius, F. A., Gage, R. P.: Life Expectancy in Angina Pectoris, J.A.M.A. **131** : 95-100, 1946.
13. Patterson, J. C.: Relation of Physical Exertion and Emotion to Precipitation of Coronary Thrombi, J. A. M. A. **112** : 895-897, 1939.
14. Sanjivi, K. S.: "Heart Disease in South India," Proceedings of the Annual Conference of the Association of Physicians India.
15. Vakil, R. J.: A Study of Rheumatic Heart Disease in Bombay Province, Indian Heart Journal, **1** : 15-46, 1949.
16. White, P. D. and Bland, E. F.: Further Report on Prognosis of Angina Pectoris and Coronary Thrombosis, Am. Heart J. **7** : 1-14, 1931.
17. White, P. O., Bland, E. F., and Miskall, E. W.: Prognosis in Angina Pectoris Long Term Follow-up of 497 Cases, J. A. M. A. **123** : 801-804, 1943.
18. Yater *et al.*: Coronary Artery Disease in Men of 18 to 39 Years of Age, Report of 866 Cases, Am. Heart J. **36** : 334-372 and 481-526, 1948.

ORIGINAL ARTICLE

CEREBRAL VASCULAR ACCIDENTS

Lt. Col. Najib Khan & A. V. N. Rao *

During the period of 4 years from 1947—50, 116 cases of apoplexy due to cerebral vascular accidents were admitted to the Tata Main Hospital, Jamshedpur. Thus the incidence of cerebral vascular accidents among the population of 200,000 for which Tata Main Hospital caters is 0.4/thousand per year. The cerebral vascular accidents formed 0.58 per cent of total admissions of medical cases.

Sex :— Male—79. Female—37.

The higher number of males may give an erroneous impression but when it is borne in mind that total admissions of medical cases to the hospital of male and female are in the ratio of 2.8: 1; there appears to be no preponderance of cerebral vascular accidents in either sex.

*Age :—*Thirty per cent of the cases were below 40 years, 60 per cent between 40—60 years and 10 per cent over 60 years. However, 70 per cent of the cases among males occurred in the 40—60 age group, and only 9 per cent in the over 60 age group, whereas in females there were 25 per cent in the 40—60 age group and 25 per cent among the over 60 group. (Table 1).

TABLE 1. *Age Distribution of Cases.*

Age Group.	Total No.		Male. No.		Female. No.	
20—30 Years	11		6		5	
30—40 ,, ...	23	(30%)	18	(33%)	5	(25%)
40—50 ,, ...	35	(39%)	25	(58%)	10	(25%)
50—60 ,, ...	25	(21%)	16	(20%)	9	(25%)
60—70 ,, ...	8		2		6	
70—80 ,, ...	3		2		1	
80—90 ,, ...	0	(10%)	0	(7%)	0	(25%)
90—100 ,, ...	0		0		0	
100—110 ,, ...	1		0		1	
	116		79		37	

*Mode of Onset :—*At the time of onset the patients were asleep in approximately 1/6th, at rest in approximately 1/2 the cases and walking in another 1/6th. The relation to passing stool is an interesting point which was noticed in 1/9th, and only 1/10th had cerebral vascular accidents while at work. (Table 2).

---

* Department of Medicine, Tata Main Hospital, Jamshedpur.

TABLE 2. *Onset of Accident.*

	Total.	Thrombosis.	Hæmorrhage.	Embolism.	Other group.
Sleeping	20	19	1	..	..
Rest..	53	21	19	5	8
Walking	15	9	6	..	..
Cycling	3	2	..	1	..
Working	11	8	3	..	..
In the W. C. ..	14	3	10	..	1
Total ..	116	62	39	6	9

Side of Lesion :—Analysis of 70 non-fatal cases of cerebral hæmorrhage, thrombosis and embolism revealed that 39 had left sided and 31 right sided cerebral lesions. Of these, 70.24 (34.3 per cent) cases had aphasia. Of the 24 cases of aphasia, 22 had left sided lesions and 2 right sided lesions. Of the 39 cases with left sided lesions, 56.4 per cent had aphasia and of the 31 with right sided brain lesions, 6.4 per cent had aphasia. The 2 cases of right sided lesions exhibiting aphasia were most probably left handed.

Coma :—At the time of cerebral vascular accidents, 54 per cent lost consciousness and coma varied from 1 hour to 7 days. Of those who developed coma, 43 per cent were unconscious for more than 1 day, 34 per cent for more than 2 days and 16 per cent for more than 3 days. All those who were unconscious for more than 3 days died. In the case of cerebral thrombosis all those who were unconscious for over a day died.

TABLE 3. *Period of Coma.*

	Fatal cases.	Thrombosis.		Hæmorrhage.		Embolism.		Other Groups		All cases.
		Total.	Fatal.	Total.	Fatal.	Total.	Fatal.	Total.	Fatal.	
Nil. ..	2	47	0	1	0	4	1	1	1	53
1 Hour ..	1	2	1	2	0	0	0	1	0	5
2 Hours. ..	0	0	0	4	2	1	1	1	0	6
4 Hours. ..	1	3	1	0	0	0	0	0	0	3
6 Hours. ..	4	1	0	6	4	0	0	1	0	8
12Hours ..	4	1	1	3	3	0	0	0	0	4
1 Day ..	6	5	2	5	4	0	0	0	0	10
2 Days ..	6	1	1	4	3	0	0	3	2	8
3 Days ..	6	1	1	9	5	0	0	0	0	10
4 Days ..	2	0	0	1	1	0	0	1	1	2
5 Days ..	1	0	0	0	0	0	0	1	1	1
Over 5 days	6	1	1	4	4	1	1	0	0	6
Total ..	42	62	8	39	26	6	3	9	5	116

Glycosuria :—In 8 per cent glycosuria was discovered at the time of admission. On further investigation of these cases it was found that only 3 per cent were true cases of diabetes-mellitus and the other 5 per cent were not.

It is not always easy to diagnose the exact lesion in every case of cerebral vascular accident, but, as advocated by Aring and Merritt[1], an attempt should always be made to differentiate the lesion. The criteria that we applied for the diagnosis of different lesions of cerebral vascular accidents may briefly be stated :—

Cerebral Hæmorrhage :—Sudden onset accompanied by unconsciousness in a hypertensive individual with arterial disease and on lumbar puncture blood intimately mixed with the cerebro-spinal fluid.

Cerebral embolism :—Sudden onset with known source of embolism and lumbar puncture revealing clear cerebro-spinal fluid.

Cerebral thrombosis :—Less dramatic onset with no blood in the cerebro-spinal fluid.

Type of Lesion :—Cerebral thrombosis is the commonest accident *i.e.*, 64 cases (54.4 per cent). The other lesions in order of frequency were, cerebral hæmorrhage 39 (33.6%), cerebral embolism 6 (5.2%), sub-arachnoid hæmorrhage 3, pontine hæmorrhage 2, hypertensive encephalopathy 2, subdural hæmatoma and cavernous sinus thrombosis each 1. (Table 4).

TABLE 4. *Types of Lesions.*

Type.	Total.	Male.	Female.
Cerebral Thrombosis	64 (54.4%)	46 (58%)	16 (43.2%)
,, Hæmorrhage	39 (33.6%)	23 (29.1%)	16 (43.2%)
,, Embolism	6 (5.2%)	2 (2.5%)	4 (10.8%)
Sub-arachnoid Hæmorrhage	3	3	..
Pontine Hæmorrhage	2	1	1
Hypertensive Encephalopathy ..	2	2	..
Subdural Hæmatoma	1	1	..
Cavernous Sinus Thrombosis ..	1	1	..
Total ..	116	79	37

Fatalities :—Of the 116 cases, 42 died giving the mortality rate of 36.2 (37.2% in the male and 35.1% in the female). Deaths due to cerebral vascular accidents formed 5 per cent of the total medical deaths in the hospital per year.

TABLE 5. *Distribution of Fatalities According to Lesion.*

Lesion.	Total.	Male.	Female.
Cerebral Thrombosis	8 (12.9%)	6 (13.1%)	2 (12.5%)
,, Hæmorrhage	26 (66.6%)	16 (69.6%)	10 (62.5%)
,, Embolism	3 (5%)	2 (100%)	1 (25%)
Sub-Arachnoid Hæmorrhage	2	2	..
Pontine Hæmorrhage	1	1	..
Sub-dural Hæmatoma	1	1	..
Cavernous Sinus Thrombosis ..	1	1	..
Total ..	42 (36.2%)	29 (37.2%)	13 (35.1%)

Recovery :—32 male cases were subsequently followed up after discharge from hospital. From them one went to his job immediately on discharge, 5 recovered within a period of 6 months to 1 year and resumed their previous occupations. All cases were assessed after 1 year when 11 were incapacitated for any work, the remaining 15 are still unfit.

Of the total 116 cases of cerebral vascular accidents, cerebral hæmorrhage, thrombosis and embolism were responsible for all except 9 cases. Therefore the study of these three types of lesions may be instructive.

TABLE 6. *General Review* (107 *Patients*).

	Thrombosis.	Hæmorrhage.	Embolism.
Cases	62	39	6
Percentage of total cerebral vascular accidents ..	54·4%	33·6%	5·2%
Deaths	8 (12.9%)	26 (66.6%)	3 (50%)
Male cases	46	23	2
Female cases	16	16	4
Average age	47·3 (70–25)	49.8(103-35)	30.3 (48-20)
Average B. P.	180/108 (300/190–120/60)	195/116 (280/190–150/75)	155/96 (180/130–130/60)
W. R. Positive ..	35·3%	11.1%	0%

CEREBRAL THROMBOSIS (62)

Cerebral thrombosis formed 54.4 per cent of the total cerebral vascular accidents being 58 per cent in males and 43 per cent in females. Average age was 47.3 years, the youngest being 25 years and the oldest 70 years. Approximately 55 per cent were in 40—60 group and approximately 30 per cent amongst the below 40 group, there being none over 70 years. The average B. P. was 180/108 with the maximum tension of 300/190 and the minimum of 120/60. At the time of onset of thrombosis, 33 per cent were asleep and the same number were at rest, there being only 10 per cent who were at work. At the onset only 20 per cent had any disturbance of consciousness and amongst them the period of coma was from 1 hour upto 6 days. The period of coma exceeded over one day in three cases only and all these died. Cerebrospinal fluid in 50 per cent had increased protein and in 40 per cent increased cells. The average C.S.F. protein was 53 mg. per 100 c.c. and average cells 48 per c.mm. C.S.F. Wassermann was positive in 25 per cent of cases and in those protein was increased in 50 per cent and cells in 39 per cent. Blood Wassermann test was positive in 35.3 per cent. The mortality rate was 12.9 per cent. The mortality in the 20—40 age group was 7 per cent, 40—60 age group 15 per cent and no death in those over 60.

CEREBRAL HÆMORRHAGE (39)

Cerebral hæmorrhage comprised 33.6 per cent of the total cerebral vascular accidents, being 29.1 per cent in males and 43.2 per cent in females. The average age was 49.8 years, the oldest being 103 years and the youngest 35 years. The maximum incidence was in the 40—60 age group (59%), 22 per cent were in the under 40 age group and 19 per cent over the 60 age group. The average B. P. was 195/116 with the maximum of 280/190 and the minimum of 150/75. At the time of occurrence of hæmorrhage 50 per cent were at rest, 3 per cent asleep, 15 per cent walking, 7 per cent working and approximately 15 per cent gave a definite relationship with passing of stool. All the patients became unconscious at the time of occurrence of hæmorrhage and the period of unconsciousness lasted upto 7 days. The period of coma lasting over 3 days was seen only in 13 per cent and all of them expired. Blood Wassermann was positive in 11.1 per cent and C.S.F. in all cases was tinged with blood. The mortality was 66.6 per cent being 86 per cent in the over 60 age group, 70 per cent in the 40—60 age group and 46 per cent in the below 40 group.

TABLE 7. *Distribution of Different Lesions in Age Groups.*

Age Group.	Thrombosis.		Hæmorrhage.		Embolism.	
	Total.	Fatal.	Total.	Fatal.	Total.	Fatal.
20—30 Years ..	4	1	0	0	4	1
30—40 ,, ..	10 (30%)	0 (7%)	9 (22%)	4 (46%)	1	1
40—50 ,, ..	30	5	13	11	1	1
50—60 ,, ..	14 (55%)	2 (15%)	10 (59%)	5 (70%)	..	..
60—70 ,, ..	4	0	3	2	..	..
70—80 ,, ..	..	..	3	3	..	..
80—90 ,, ..	.. (0%)	.. (0%)	.. (19%)	.. (86%)	..	..
90—100 ,, ..	..	..	..	..		..
100—110 ,, ..	..	..	1	1	..	..
Total	62	8	39	26	6	3

CEREBRAL EMBOLISM (6)

Cerebral embolism formed 5.2 per cent of the cerebral vascular accidents, being 2.5 per cent in males and 10.8 per cent in females. The average age was 30.3 years, the oldest being 48 years and the youngest 20. At the time of occurrence of the embolism 83 per cent were resting and 34 per cent of the cases became unconscious. The average B. P. was 155/96 with the maximum of 180/130 and minimum of 130/60. C.S.F. was normal in all cases and blood Wassermann negative. Of the six cerebral embolism cases, one resulted from coronary thrombosis, one from rheumatic disease of the heart and four were females after septic abortion.

HYPERTENSIVE ENCEPHALOPATHY

Two cases of hypertensive encephalopathy were seen: They were both obese males aged 40 and 65 years, and both were diabetic. The onset was sudden and while at rest. One had coma for an hour and the other presented hemiparesis. At the time of admission they had no acetonuria. The man aged 40 who had only unconsciousness, had a second attack after an interval of an year. In both cases blood Wassermann was negative and C.S.F. was normal.

Similar investigations in the U.S.A. by Gilbert and De' Takats[2] who studied 121 cases over a period of 6 years is summarised in Table 6 (a).

TABLE 6 a. 121 *Cases of Gilbert & De'Takats (U.S.A. Figures).*

	Thrombosis.	Hæmorrhage.	Embolism.
Cases	53	53	15
Percentage	43.8%	43.8%	12.4%
Average Age	69.9 (40–82)	58.9 (41–81)	53.1 (18–80)
Males	32	33	12
Females	22	20	3
Average B. P.	166/97 (205/140–120/70)	213/120 (300/150–129/70)	148/85 (210/110–110/80)
Onset	Sudden (47%) Gradual (55%)	Sudden (92%) Gradual (8%)	Sudden (100%) ..
Deaths .. : ..	24%	77%	40%

Comparison with the U. S. A. study reveals that in America cerebral thrombosis and hæmorrhage each formed 43.8 per cent of the total cerebral vascular accidents as compared with our figures of 54.4 per cent and 33.6 per cent respectively, whereas cerebral embolism in the U.S.A. formed 16 per cent as compared to 5.2 per cent in our series. The average age in U. S. A. patients was much above our series, being 22 years higher for cerebral thrombosis, 9 years for cerebral hæmorrhage and 23 years for cerebral embolism. In our series the average age for cerebral thrombosis and hæmorrhage is pretty nearly the same but in the U.S.A. series the average age of cerebral thrombosis is 11 years more than that for cerebral hæmorrhage. The average blood pressure in our series like the American series is highest for cerebral hæmorrhage and lowest for cerebral embolism, thrombosis being in between. The mortality in our series is however much less than in the American series; especially for cerebral thrombosis, where the mortality in our series is only half of that of the American series.

SUMMARY AND CONCLUSIONS

A study of 116 cases of cerebral vascular accidents admitted to Tata Main Hospital over a period of 4 years is given. From the study the following conclusions may be drawn.

1. The incidence of cerebral vascular accidents is 0.4/thousand.
2. Both sexes are equally affected.

3. Highest incidence of cerebral vascular accidents occurred in 40—60 age group, though under 40 group is not free from the hazard of cerebral vascular accidents, there being 1/3rd of the cases in that group.

4. Only 9 per cent had cerebral vascular accidents at work and 66 per cent were at rest while the accident occurred. There was a definite relationship with passing stool in 15 per cent of the cases.

5. At the time of onset approximately half the cases lost consciousness.

6. Coma lasted over 1 day in 20 per cent of cases and over 3 days in 3 per cent.

7. Coma over 1 day in cerebral thrombosis and over 3 days in cerebral hæmorrhage always ended fatally.

8. Mortality rate was 36.2 per cent being 37.2 per cent in males and 35.1 per cent in females.

9. The commonest lesion was cerebral thrombosis.

10. In the females cerebral thrombosis and cerebral hæmorrhage were equal.

11. Average age for cerebral hæmorrhage was 49.8 years, for cerebral thrombosis 47.3 years and for cerebral embolism 30.3 years.

12. Highest average blood pressure (195/106) was in cerebral hæmorrhage, next highest (180/110) in cerebral thrombosis and least in cerebral embolism (155/96).

13. At the time of onset, loss of consciousness occurred in cerebral hæmorrhage in 100 per cent, in cerebral embolism in 66 per cent and cerebral thrombosis in 20 per cent of the cases.

14. Death rate was highest in cerebral hæmorrhage (66.6%), next highest in cerebral embolism (50%) and least in cerebral thrombosis (12.9%).

15. Specific disease was present in 35.3 per cent of cerebral thrombosis and only 11 per cent of cerebral hæmorrhage.

16. C.S.F. was blood-stained in all cases of cerebral hæmorrhage and clear in all cases of cerebral thrombosis and embolism.

17. C. S. F. in cerebral thrombosis had increased protein in 50 per cent and increased cells in 40 per cent of cases.

Our thanks are due to Dr. E.N. Murty for his help in the calculation of the figures, to Mr. Kundan Singh for making the old records available and to Colonel J. R. Kochhar, the *Director of Medical and Health Services, Tisco, for permission* to use the hospital records.

REFERENCES

1. Aring, G. D. and Merritt H. H.: Differential Diagnosis Between Cerebral Hæmorrhage and Cerebral Thrombosis, Clinical and Pathological Study of 245 Cases, Arch. Int. Med. 56: 435-456, 1935.
2. Gilbert, N. C., and de,Takats, G.: Emergency Treatment of Apoplexy, J.A.M.A. 136: 659-665, 1948.

ORIGINAL ARTICLE

RETICULOCYTE VARIATION IN THE NEW-BORN

A. F. Pereira*

The presence of reticulated red cells in the peripheral blood was first demonstrated by Paul Ehrlich in 1881 by staining blood smears with saturated aqueous solutions of methylene blue. Subsequently, it was confirmed in Virchow's Archivk Pathologische Anatomie in 1899. The blood of a healthy adult contains from 0 to 2 per cent of reticulocytes and usually they are less than 1 per cent.

The circulating blood of a new-born infant contains a fair number of immature red cells both nucleated and reticulocytes, but after infancy the blood does not normally contain nucleated cells or more than 2 per cent of reticulocytes. Any increase in the number of reticulocytes or the appearance of nucleated cells indicates abnormal activity of the bone marrow. The variation of the reticulocytes from the high level on the first day of neonatal life to a gradual fall to the healthy adult level at the end of the first week has been investigated by many workers in different parts of the world and the object of my work on this problem was to find out whether in this part of the country there is any departure from the accepted figures. Krumbhar[1] lays down 0.3 per cent reticulocytes for normal adults and quotes Lee's and Minoto's figures for man as 0.8 per cent. His average for normal infants is 5 to 10 per cent and asserts that even 20 per cent should be considered as normal. Further, according to his observations, in none of the infants did it exceed 5 per cent in the first 24 hours and in none did it exceed 3 per cent after the first 24 hours. By the end of the first week, practically normal levels are reached so that with these exceptions the normal infant's reticulocytes are the same as those of adults. He further mentions the observations of Cathala and Dannay on eight infants in whom were found an increased number at birth which reached the normal level by the end of the first week although he found their figures to be distinctly lower than those of his own series.

While Krumbhar mentions that reticulocytosis is common with other hæmatological changes which occur more readily and to a greater degree in infants than during adult life, Waugh, Merchant and Maughan[3] quote Schiff (1899) as having maintained that the difference in value may be due to environment and geographic location. They have reviewed the work of Krumbhar and also refer to the observation of the following :—

Friedlander and Weidemere reported 11 per cent reticulocytes

---

* Department of Pathology, B. J. Medical College, Ahmedabad.

in the first 24 hours, the number steadily and uniformly decreasing to the eighth day when it reached adult value.

Frank mentions 1 to 9 per cent during the first week.

Seyfarth reported 0.5 per cent to 10 per cent as the range within the first few hours with a fall to 0.3 per cent to 1 per cent in six days.

Seyfarth and Jurgeus give 7 per cent at birth and 2 per cent at ten days and 0.7 per cent by three weeks.

Kato mentions 1.4 to 1.9 per cent with a maximum of 5.5 per cent and a minimum of 0.1 per cent during the first 36 hours and with a fall to 0.5 per cent after 5 days.

Goldbloom and Gottlieb found 7 per cent reticulocytes in the umbilical cord, 5 per cent on the second day, 3 per cent on the third day, 2 per cent on the fourth day, 0.5 per cent on the fifth day. They were practically absent by the sixth day. Their (Waugh, Merchant and Maughan) own observations in 1939, giving an account of 41 examinations of the blood from the umbilical cords, found an average of 2.7 per cent (range 0.2 to 5 per cent). On the second day the venous blood was examined and the average of 34 samples was 3.1 per cent (range 0.3 to 4.5 per cent). On the fourth day the average of 28 cases was 2.3 per cent with a distribution of 0.3 to 4.2 per cent. One examination of the fourth day blood of a case of erythroblastosis fœtalis was 10.6 per cent. On the sixth day 24 samples gave an average of 1.2 per cent (range 0.2 to 3 per cent), while on the ninth day the average of 22 cases was 0.34 per cent (range 0.1 to 9 per cent). Everard Napier and Das Gupta[2] working in Bengal found a mean percentage of 0.67 per cent. ± 0.37 in a series of 50 city dwelling Indian adult males with a range from 0.2 to 1.4 per cent and 0.37 per cent ± 0.27 amongst 122 women.

Present work was done as follows:—

Adopting routine hæmatological methods, blood counts were done on 20 infants born at the maternity wards of the Civil Hospital Ahmedabad. Four infants were presumably having disorders of blood as detailed in Table 1. Out of the 16 healthy infants only ten remained in the hospital to complete the examination for the whole first neonatal week. Reticulocyte count and observation for nucleated cells were done daily but the total red count was done on the first and seventh days only. No attempt was made to follow these cases clinically or by hæmatological investigation after the first week. The observations are recorded in Table 1. For arriving at the normal average reticulocyte percentage and nucleated cell percentage, figures obtained from healthy babies alone were taken into account. For the purpose of comparison, total red cell count and reticulocyte percentage of nine male healthy adults are also recorded in Table 2. Special mention should be made of infant No. 1 and infants with hæmatological disorders.

TABLE 1. *Red Cell Variation in the First Neonatal Week.*

Infant No.	Total Erythrocyte count per cubic millimeter of blood in millions.	Reticulocyte Percent During the First Seven Days.							Total Erythrocyte count per cubic millimeter of blood in millions.
		Days.							
	First day.	1	2	3	4	5	6	7	Seventh day.
1.	4.51	8 1	8.26	16	9	2.4	3.8	0.5	3.73
2.	5.53	1.33	2	1.3	0.2	0.2	0.1	0	5.9
3.	7.54	5.4 1	4.8	4.3	4.5	1.6	0.4	1.2	5.60
4.	6.32	2.4 1	2.6	0.5	0.8	1.7	0.3	0.3	5.03
5.	6.6	6.8 1.5	3.6 3	4.5	2.6	0.8	0.2	0	5.75
6.	5.6	1.8	1.9	2.4	0.8	0.7	0.9	Infant discharged.	
7.	5.52	5.4 7	2.4 1	2.5	2.1	0.9	0.7	0.8	5.10
8.	4.8	2.9	1.2	0.6	0.7	0.6	0	0	5.63
9.	5.96	4.4	0.9	1.3	0.2	Infant discharged.			
10.	7.81	2 1	2.3	3.2	1.5	0.9	0.2	0 1	5.51

11.	6.92	2.6 11	2.9 26	0.9 45	2.6 20	1.0 13	0.7 24	Expired.	
12.	6.64	1.1 2	0.9	3.1 2	0.4	0.2 2	0	0	5.60
13.	6.56	2.4	4.0 2	1.3	1 1	1	1.2	0.2	4.88
14.	5.08	3.8 29	12.4 40	10.8 89	Infant expired.				
15.	6.42	5.9 2	3 1	4	2 1	2	1.1	0.9 1	5.55
16.	6.55	3.9 2	11.9	1.7	2.1 1	0.1	Infant discharged.		
17.	6.87	11	3.1	3.2	2.0	0.6	0.2	0.3	3.43
18.	6.88	2.11 1	1.5	1.8	Infant discharged.				
19.	6.18	4	1.7	5.9	1.8	1.1	Infant discharged		
20.	7.3	3.2 1	3.3	Infant discharged					
Average :	6.38	3.44 1.21	3.0 0.43	2.56 0.13	1.47 0.21	0.9 0.15	0.46	0.34 0.2	5.45

Above total red cell counts and reticulocyte percentages. While taking the averages of all the above columns the case Nos. 1, 11, 14 and 17 where not taken into consideration.

Note :—Lower figures are of nucleated red cells. Where no figure is recorded it is to be read nil.

Premature Infants :—Infant No. 1 is the only one premature infant in which the reticulocyte count returns to normal adult figures on the seventh day, i.e., 0.5 per cent. The total red cells on the first day were 4.51 millions, the reticulocytes in the first four days ranged from 8 to 16 per cent, which rapidly fell in the last three days to normal adult level with total red cell count of 3.73 millions on the seventh day. The nucleated red cells were 1 per cent on the first day only.

Infants with abnormal nucleated red cells :—Infant No. 11 has its reticulocyte percentages low but the percentages of the nucleated red cells are abnormally high as shown in Table 1. Infant No. 14 is a case of erythroblastosis fœtalis. In it the reticulocyte percentages are higher and the percentages of the nucleated red cells for those three days being 29 per cent, 40 per cent and 89 per cent. The infants died on the third day.

Infant No. 17 showed 11 percent reticulocytes on the first day falling rapidly to 3.1 per cent on the second day and to 0.3 per cent on the seventh day. Total red cell count on the first day was 6.87 millions and on the seventh day 3.43 millions. No nucleated red cells were found throughout. The infant became jaundiced from the third day and improved with vitamin K.

DISCUSSION

The average erythrocyte count of 16 infants was found to be 6.38 millions on the first day and the corresponding percentage of reticulocytes is 3.44 per cent. The percentage of reticulocytes shows a progressive daily fall till on the seventh day it is 0.34 per cent and the corresponding total red cell count is 5.45 millions.

Whitby and Britton[4] quotes 6.5 millions to 7.25 millions of red cells on the first day and 5 millions to 5.5 millions quoted by the same authors for the twelfth day. The total red cells of nine Indian male adults is 5.28 millions and it is almost equal to the red cells of infants on the seventh day, that is, 5.45 millions.

TABLE 2. *Record of Total Erythrocytes Per Cubic Millimeter of Blood and the Reticulocyte Percentage of Nine Normal Male Adults.*

No.	Reticulocyte percentage.	Erythrocytes in millions /c.mm.
1	0	4.97
2	0.1	5.71
3	0.2	5.87
4	0.2	4.44
5	0.1	5.98
6	0	4.99
7	0.3	5.20
8	0.4	5.36
	0.1	5.00
Average	0.15	5.28

Similarly, the reticulocyte percentage of the infants on the seventh day is 0.34 per cent and those of nine Indian male adults is 0.15 per cent.

The range of nucleated red cells is 1.21 per cent in the first 24 hours and 0.16 per cent on the seventh day.

The average red cell count and reticulocyte percentage of infants as observed on the seventh day were found to be distinctly higher than those recorded in adults. This indicates that during infancy the reticulocyte percentage continues to be higher than the adult level. This observation differs from that of the majority of the previous workers on the subject. Similarly, it is found that the nucleated red cells are found in the peripheral blood upto the seventh day. Perhaps these differences may be explained on the basis of geographic location, social status, etc. It may be noted that these observations were all made on infants of poor parentage.

CONCLUSION

The average reticulocyte percentage on th first day is 3.4 per cent and after gradually decreasing from day to day the percentage on the seventh day is 0.34 per cent. The range on the first day is 1.1 to 6.8 per cent and for the seventh day it is 0 to 1.2 per cent.

Not much significance can be attached to a single observation of high reticulocyte count, since, according to Krumbhar, even 20 per cent may be taken as normal. But persistence of higher percentages may be taken as a fair index of abnormal hæmopoieses as in No. 14 of the present series.

No. 14 which was a case of erythroblastosis fœtalis showed increasing higher percentages of nucleated red cells and persistently high reticulocyte count indicating abnormal activity of the bone marrow.

Infant No. 11 showed persistently high nucleated red cell percentages but unfortunately the autopsy was not done and the bloods were not examined for Rh factor and ABO heterospecificity. It might have been a case of erythroblastosis. Thus it is clear that in suspected blood disorders of the new-born, it is very important to examine the peripheral blood of the infant for nucleated red cell percentage, for, as in No. 14, it will certainly help in the diagnosis of erythroblastosis when Rh factor tests are not feasible.

ACKNOWLEDGMENT

The writer is thankful to Dr. H. I. Jhala, M. D., Professor of Pathology, B. J. Medical College, Ahmedabad, under whose direction this work was done.

REFERENCES

1. Krumbhar E. B.: Reticulosis, Increased Percentage of Reticulated Erythrocytes in the Peripheral blood, Journal of Laboratory and Clinical Medicine, **8**: 11-18, 1922.
2. Napier, E. L., and Das Gupta C. R.: Hæmatological Technique, pp. 41, Thacker, Spink & Co., Ltd., Calcutta 1941.
3. Waugh T. R., Merchant F. T., and Maughan C. B.: Blood Studies on the New born, American Journal of Medical Science, **198**: 646-665, 1939.
4. Whitby, L. E. H., and Britton C. J. C.: Disorders of the Blood, pp. 337, J. & A. Churchill Ltd., London, 1947.

ORIGINAL ARTICLE

THIAMINE AND RIBOFLAVIN CONTENT IN THE TISSUES OF SOME SALT WATER FISHES IN BOMBAY

Vidya Pradhan and R. G. Chitre *

Considerable work has been done both in Europe and America on the nutritive value of fish[1, 4, 5, 7, 8, 11, 13, 18]. In India, Guha and others have collected a data on the nutritive value of fresh water fish in Bengal[9, 10]; Basu, Sircar and Gupta[2]; De, Majumdar and Sanderarajan[6] and Chari[3] have worked on fishes in Madras. Niyogi *et al*[14] and Setna *et al*[15] have worked on the nutritive value of fish of the Bombay harbour. These investigations have primarily restricted themselves to the studies of proximate principles, minerals, vitamin A and nicotinic acid content of fish.

Drummond[7] found protein extracts of whole fish a good source of vitamin B_1 and were valuable for good growth. Chick and Hume[4] showed that fish ova is a rich source of thiamin. Klocke[13] found that fishes of Michigan waters are rich in vitamins of the B complex. Hoaer *et al*[11] have worked on the distribution of riboflavin in fresh and processed fish and have shown that the riboflavin content is lower than that of the glandular organs of mammals.

In India very little work has been done on the content of vitamins of the B complex in fish. The thiamin and riboflavin content of tissues of some common fish in the Bombay harbour is reported in this paper.

METHODS AND MATERIALS

The fishes selected for the study are those which are common in Bombay waters and are largely consumed by local populations. They were brought from the Bombay Market chilled in ice in as fresh a condition as possible. The different organs were separated and weighed. Thiamin and riboflavin were estimated on aliquots of tissues by the methods of Holmann[12] and of Slater and Morell[16], respectively. Five samples of each fish were analysed. In Table 1 and 2 are given the zoological and common names of the fish together with the average thiamin and riboflavin contents of the different tissue in mg. per 100 Gm. of fresh tissue.

DISCUSSION

From the Table Nos. 1 and 2 it could be seen that heart, liver, spleen and glands are rich sources of thiamin; muscle, however, is poor in the vitamin. It is likely that the lower content of thiamin in this tissue

---

* Department of Physiology, Biochemistry Section, Seth G. S. Medical College, Parel, Bombay 12.

TABLE 1. *Thiamine Content in mg/100 Gm. of Fresh Tissue.*

Scientific name of the fish.	Local name.	Heart.	Liver.	Spleen.	Gonads.	Muscle.
Stromateus, cinnereus	Pomphret	8.75	8.40	8.90	20.84	3.32
Coilea, dussumerii	Mandeli	364.90	164.60	..	13.88	23.92
Sciena glanca	Dhami	23.05	16.35	67.45	1.51	3.42
Rastrelliger karagurta	Bangra	32.56	33.05	..	67.14	16.51
Horpedon nehercus	Bombay duck	58.87	56.01	240.90	29.45	6.76
Mugil kalaartii	Boya	39.98	25.59	47.71	34.61	7.79
Scoliodon sorrakewa	Mushi	4.31	4.20	15.89	116.70	4.50

TABLE 2. *Riboflavin Content in mg./100 Gm. of Fresh Tissue.*

Scientific name of the fish.	Local name.	Heart.	Liver.	Spleen.	Gonads.	Muscle.
Stromateus, cinnereus	Pomphret	1.77	2.56	2.49	2.67	0.55
Coilea, dussumerii	Mandeli	35.83	12.89	..	16.01	2.12
Sciena glanca	Dhami	10.34	6.52	30.35	1.50	2.47
Rastrelliger karagurta	Bangra	3.67	1.23	..	1.45	2.83
Horpedon nehercus	Bombay duck	56.03	16.14	..	1.20	3.12
Mugil kalaartii	Boya	5.88	2.46	9.80	9.68	2.90
Scoliodon sorrakewa	Mushi	1.98	3.35	3.62	46.67	1.13

may be due to the presence of the thiaminase in larger concentration and that some amount of vitamin was destroyed during the interval between the catch of the fish and the analysis of the tissues. This may be true only when it is found that other tissues are comparatively poor in thiaminase. The investigation in this direction is in progress.

As regards riboflavin, the same is practically true with the exception of the gonads which are very poor in this vitamin. The level of this vitamin content is however much lower in the tissues than that of thiamin.

The thiamin and riboflavin content of different tissues showed a great variation. It may be either due to the difference in metabolic activity of the tissues or the time of the season when the catch was effected. A further study has been undertaken to note the seasonal changes in the vitamin contents of the tissues. The results will form a part of a future publication.

SUMMARY

Seven varieties of salt water fish available in Bombay waters were investigated for their thiamine and riboflavin content in different tissues.

It was found that the tissues like, heart, spleen and gonads were rich in this vitamin while the muscle was comparatively poor. This was probably due to the presence in greater concentration of the thiaminase in this tissue than in others.

The same was practically true as regards the riboflavin content of the tissues with the exception of gonads which were very poor in this vitamin. The vitamin contents showed considerable variations in different samples. This was probably due to the seasonal changes in the metabolic activity of the tissues.

REFERENCES

1. Atwater, W. O.: Quoted from Allen's Commercial Organic Analysis. **9**: p 575, London, J. & A. Churchill, 1932.
2. Basu, K. P., Rai Sircar, B. C. and Sen Gupta, J. C.: Vitamin A Content of Some Species of Bengal Fish by Biological, Tintometric and Spectroscopic Methods. Ind. Jour. Med. Res. **27**: 721-729, 1940.
3. Chari, S. T.: Nutritive Value of Some of the West Coast Marine Food Fishes from Madras Province. Ind. Jour., Med. Res. **36**: 253-259, 1948.
4. Chick, H. and Hume M.: Quoted from Quantitative Experiments on the Occurrence of Vitamin B in Organs, Brodie, J. B. and F. Macleod, Jour. Nutrition, **10**: 79-186, 1935.
5. Clark, E. D. and Almy, L. H.: A Chemical Study of Food Fishes, Jour. Biol. Chem. **33**: 483, 1918.
6. De, N. K., Majumdar, B. N. and Sanderarajan, A. R.: The Vitamin Activity of Some Fish Oils and Vegetable Food, Ind. Jour. Med. Res. **26**: 435-440, 1938.
7. Drummond, J. C.: Quoted from Quantitative Experiments on the Occurrence of Vitamin B in Organs, Brodie, J. B. and F. Macleod. Jour. Nutrition, **10**: 179-186, 1935.

8. Gibbs, W. E.: Quoted from Allen's Commercial Organic Analysis, **9**: 585, London, J. & A. Churchill, 1932.
9. Ghosh, A. R. and Guha, B.C.: Investigations on the Nutritive Values of Indian Food Stuffs. Ind. Jour. Med. Res. **21**: 761-768, 1934.
10. Guha, B. C. and Chakravarty, P. N.: Further Observations on Vitamin B2, Ind. Jour. Med. Res. **21**: 211-219, 1933.
11. Hoaer, W. S. and Barberic, M.: Distribution of Riboflavin in Fresh and Processed Fish, Canad, J. Res. **23**: 8-18, 1945.
12. Holmann, W. I.: Estimation of Aneurin by Thiochrome Method, Biochem. Jour. **38**: 388, 394, 1944.
13. Klocke, J. F.: Nutritive Value of Fish from Michigan Waters, Food Res. **12**: 36-43, 1947.
14. Niyogi, S. P., Patwardhan, V. N., Acharya, B. N. and Chitre, R. G.: Studies on the Nutritive Value of Fish. Balanced Diets Part II, Ind. Jour. Med. Res. **29**: 279-285, 1941.
15. Setna, S. B., Sarangdhar, P. N., and Ganpule, N. V.: Nutritive Values of Some Marine Fishes of Bombay, Ind. Jour. Med. Res. **32**: 171-176, 1944.
16. Slater, E. C., and Morell, D. B.: A Modification of the Fluorometric Method of Determining Riboflavin in Biological Materials, Biochem. Jour. **40**: 644-652, 1946.
17. Swaminathan M.: Vitamin B1 (Thiamin) Content of Indian Food-stuffs, Ind. Jour. Med. Res. **34**: 289-297, 1946.
18. Williams, H. E.: Quoted from Allen's Commercial Organic Analysis, **9**: 283, London, J. & A. Churchill, 1932.

ERRATA

In the article AUREOMYCIN IN ENTERIC FEVER, *Preliminary Communication, by* **B. B. Yodh** and **B. J. Vakil**, on page 561, in Table 4, under the heading of concentration of Aureomycin per c.c. of broth, mgm. should be read as microgms (μ) and on page 562, in the 4th paragraph, 17th line, 80 mg. should be read as 80 microgms (μ) per c.c.

MEDICAL PROGRESS

THE SURGICAL TREATMENT OF PORTAL HYPERTENSION

A REVIEW

E. J. Borges *

In recent years there has been considerable interest in surgical methods of treating portal hypertension, and several novel procedures have been advocated and practised. It is the purpose of this article to review the literature that has appeared on the subject.

Portal hypertension results from obstruction to the portal venous system. This obstruction may be in the liver, the result of hepatic disease, or outside the liver. Intra-hepatic obstruction is most commonly due to cirrhosis of the liver, and this is responsible for over 80 per cent of cases of portal hypertension met with in practice. Extra-hepatic obstruction may result from various causes. These have been classified by Whipple[24] and later by Linton[11], into congenital and acquired types. The congenital type is represented by obliteration, stenosis, and atresia of the portal vein which starts in infancy. The acquired variety may be the result of thrombosis, abdominal injury followed by fibrosis, and the pressure of tumors and other masses in the abdomen.

The consequence of portal obstruction is back pressure, and as the portal system of veins has no valves, this pressure is passed on to all the tributaries, giving rise to dilatation of all collateral routes, enlargement of the spleen, and varicosities. Thus are formed internal hæmorrhoids and gastro-esophageal varices. Bleeding from the latter may be very serious and lead to death, particularly in subjects of hepatic cirrhosis who are debilitated and have poor liver function.

However, it is not every case of portal hypertension that is complicated by bleeding from esophageal varices. The reason for this lies in the inconstant nature of the anastomosis between the portal and systemic circulations at the cardio-esophageal area. Kegaries[10] in 1934 showed by careful injection studies that there exists in the submucous and submuscular planes fine anastomotic channels between the gastro-cardiac veins and the lower esophageal veins. In some cases the anastomotic network is poorly developed. It is in these cases of ill developed anastomoses that esophageal varices are not likely to form, whilst portal hypertension arising in subjects with a rich anastomotic network is likely to result in varices.

When bleeding from esophageal varices has occurred the case becomes a serious problem. Linton[12] has found that in 36 per cent of these patients bleeding is fatal. According to Blakemore[2], a patient of liver cirrhosis who has bled from esophageal varices once has only a 50 per cent chance of being alive after one year. From this it follows that esophageal bleeding, once it has occurred, calls for some treatment that will remove the varices or reduce the pressure in the portal system. Various methods of treatment have been in use and new ones have been devised. They may be classified as follows :—

---

* Department of Surgery, Tata Memorial Hospital, Bombay.

1. *Encouraging the formation of new collaterals.*
    - (*a*) Omentopexy (Talma-Morison).
    - (*b*) Mediastinal packing (Garlock and Som).
2. Reducing portal circulatory volume.
    - (*a*) Splenectomy.
    - (*b*) Ligation of splenic artery.
3. Attacking the varices or site of bleeding directly.
    - (*a*) Sclerosing injections.
    - (*b*) Pressure.
    - (*c*) Ligation of gastric vessels.
    - (*d*) Gastric transection and re-suture (Tanner).
    - (*e*) Cardio-esophageal resection.
    - (*f*) High gastric resection or total gastrectomy.
4. Large venous shunt operations.
    - (*a*) Spleno-renal shunt.
    - (*b*) Porta-caval shunt.

OMENTOPEXY

Talma[20] in Holland (1898) and Rutherford Morison[15] in England (1895) independently attempted to treat cirrhosis of the liver with ascites by trying to establish new collateral vessels by attaching the omentum to the anterior abdominal wall. This procedure with its modifications is referred to as the *Talma-Morison* operation. The surfaces of the liver and spleen are also vigorously rubbed to promote adhesions to, and new vascular channels through, the diaphragm and parieties. The immediate mortality of this operation is about 15 per cent and if the cases are properly selected symptomatic relief of ascites, etc., occurs in a small percentage of cases (Grey Turner)[22]. However, many patients fail to improve because the adhesions and new vascular channels that form are feeble and not adequate enough for relief of hypertension, and so the operation is rarely performed to-day.

MEDIASTINAL PACKING

That packing the mediastinum with *gauze might result in* cure of bleeding from esophageal varices was accidentally discovered at the Mount Sinai Hospital, New York City in 1941. A patient with these varices suffered a perforation of the cervical esophagus during esophagoscopy. The posterior superior mediastinum was drained through a cervical incision and gauze packing introduced. The patient recovered and had no subsequent attacks of hæmorrhage for over the eight years that he was followed[9]. Apparently the packing resulted in the formation of granulation tissue in the para-esophageal region, and the new blood vessels so created helped to carry away the blood from the varices and remove some of the load on the portal circulation. Garlock and Som[9] have recently published their experience with mediastinal packing used for this purpose. In 8 patients so treated, there were two failures, and six satisfactory results. In the early cases only packing of the postero-superior mediastinum was done, but subsequently the authors have extended the operation to include packing of the entire posterior mediastinum from the aortic arch to the diaphragm at a second stage.

At the first stage a left oblique cervical incision is made along the anterior border of the sternomastoid muscle and the lateral and posterior surfaces of the esophagus separated from the prevertebral fascia as far down as possible. Into the space so created dry plain gauze is lightly packed, one end of which emerges from the lower angle of the cervical incision. The packing is removed after 10 days without much difficulty.

The second stage is attempted in selected patients as the operation is of some magnitude. The chest is entered through the bed of the resected seventh rib on the right side. A longitudinal incision is made along the mediastinal pleura over the esophagus, the pleural flaps are preserved while the esophagus is freed from its bed. Three strips of one inch wide single thickness gauze packing are placed longitudinally along the esophagus. A channel is then bluntly dissected between the parietal pleura and the thoracic cage, and the long ends of three pieces of gauze are withdrawn beneath the lateral flaps of mediastinal pleura through this channel to the exterior by way of a stab wound. The mediastinal pleural flaps are stitched together and the chest is closed without drainage. The packing is slowly removed without difficulty after 12 to 14 days, with the patient anaesthetised.

Garlock and Som feel that in cases of hæmatemesis associated with portal hypertension, the simpler operation of mediastinal packing in one or two stages would be worth trying before considering the more hazardous and complicated venous shunts.

SPLENECTOMY AND LIGATION OF SPENIC ARTERY

The spleen contributes a large volume of blood to the portal circulation. It has been estimated[23] that about 20 to 40 per cent of portal blood comes from the spleen. Removal of the spleen, therefore, tends to reduce the portal blood volume, and at the same time severs the short gastric veins that directly feed the varices. It was Banti in 1894 who first suggested splenectomy to cure hæmatemesis in cases of cirrhosis with splenomegaly and splenic anæmia. The term Banti's disease however, is now applied to a condition which primarily begins with a thrombosis of the splenic vein and results in splenomegaly and splenic anæmia going on to hepatic cirrhosis with a fatal termination. Splenectomy is successful in controlling hæmatemesis in Banti's disease in a large percentage of cases. Pemberton and Kiernan[16] have reported 208 cases of splenic anæmia of whom 173 had experienced one or more attacks of hæmatemesis. They were all treated by splenectomy. The survival rate after operation for five years, was in these cases, 54.8 per cent, and for 10 years, 42 per cent. We have experience of only 3 patients with Banti's disease who were all treated by splenectomy. There has been no recurrence of bleeding in one case for over 4 years.

In some cases the liver cirrhosis may be well advanced and the liver function and general condition of the patient very poor, thus making any major operation a risky one. For these cases a simple ligation of the splenic artery often suffices to tide them over a critical period. The spleen gradually atrophies after the ligation, and a sort of functional splenectomy results. Cole *et al.*[7] recommend this operation in bad risk cases.

Together with splenectomy in some cases a spleno-renal shunt operation may be combined. This operation will be discussed later.

DIRECT ATTACK ON VARICES

Sclerosing Solutions :—Direct injection of the varices with sclerosing solutions through the esophagoscope has been advocated. Although logically, the procedure appears to be unsound, in as much as one attempts to obliterate collaterals that nature has provided to drain the portal system, those who have used the method have reported satisfactory results. Moersch[14] of the Mayo Clinic has recorded 22 cases so treated. In more than half the number there was no recurrence of bleeding from 3 to 7 years after the injection treatment. In the only case we had the occasion to use this procedure, the bleeding was controlled for one year, after which the patient succumbed from uncontrollable hæmatemesis.

Local Pressure :—The first aid principle of stopping bleeding by the use of local pressure at the bleeding site has been used in these cases. Rowntree[18] has described a method which was successful in one case. He used the Miller-Abbott tube with the balloon shifted a little higher up the tube. The tube is then passed and adjusted so that the balloon lies at the lower end of the esophagus. Distending the balloon causes local pressure to bear on the bleeding area.

Ligation of Gastric Vessels :—Bleeding from esophageal varices might also be checked by ligating the feeding vessels, the short gastric veins on the greater curvature, and the left gastric vein. This operation is seldom done alone, forming as it does, a step in the operation of splenectomy. But in a poor risk case it may conceivably be done as a hurried procedure.

Tanner[21] has advocated ligation of the vasa-brevia together with a high transection and resuture of the stomach to interrupt the venous feeders to the varices. After transection of the stomach, the upper stump is raised and this facilitates exposure and ligation of all veins on the posterior aspect of the stomach. The left gastric vein is sectioned, but the left gastric artery is preserved to maintain the blood supply of the stomach.

Cardio-esophageal Resection:—Phemister and Humphreys[17] have performed an excision of the varices-bearing area as a direct attack on the bleeding site. Cardio-esophageal resection and total gastrectomy have been used by them. The follow up of their cases has not been long enough to correctly evaluate the procedure, but one feels that very few patients would qualify for this approach to the problem because the operation is rather formidable for patients with poor liver function.

High Gastric Resection and Total Gastrectomy:—Baronofsky[1] and Wangensteen believe that the cause of hæmorrhage from the varices is that the mucous membrane at this site is more vulnerable to the acid of the gastric juice because of venous stagnation in these areas. They have tried to remove the acid factor by performing a high gastrectomy or total gastrectomy in 8 patients. There was a mortality of 50 per cent and the follow up of the rest is too short for evaluation. A total gastrectomy would disconnect the esophagus from the gastric veins. But a new system of varices may develop at the jejuno-esophageal anastomosis. Altogether these operations appear to be too drastic for regular use in these cases when other measures are available.

VENOUS SHUNT OPERATIONS

The first porta-caval shunt operation was performed as an experimental measure in dogs by the Russian physiologist Nikolai Eck[8] in 1877. Ever since then surgeons have been interested in the clinical application of this principle for the relief of portal hypertension. Various attempts were made but success was not achieved until Blakemore[2] and his associates in 1945 devised an operative procedure which made the anastomosis easy to perform. Their method consisted of the use of a vitallium tube lined by a venous graft which prevented thrombosis at the anastomosis. The tube was used to produce an anastomosis between the splenic and renal veins after both the spleen and left kidney were removed, or a direct communication between the portal vein and the inferior vena cava.

Spleno-renal Anastomosis:—The spleen is mobilised, separated from the pancreas and the colon, and the short gastric veins ligated. The splenic vein is isolated, taking care to preserve its full length. The splenic artery is tied and the vein severed close to the spleen. The latter is removed. The splenic vein is separated from the pancreas by ligating the short pancreatic veins. At least 8 centimetres of the vein are necessary for the anastomosis. A rubber covered clamp controls the proximal end of the vein. The kidney is exposed transperitoneally and the renal vein isolated. The kidney is then removed. The splenic vein is passed through a vitallium tube and the end rolled back over the tube like a cuff. The cuff end of the tube is then inserted into the end of the renal vein which has already been controlled by a rubber clamp. The tube is fixed in place by a silk ligature. In this way the intima of the splenic vein is brought into contact with the intima of the renal vein, and so the chances of local thrombosis are reduced.

Porta-caval Anastomosis :—Through a right paramedian incision the portal vein is mobilised from the bifurcation at the liver to the origin of the splenic vein. Mobilisation of the duodenum to the left helps considerably. A rubber clamp is placed on the vein near the origin of the splenic, and the vein divided near the liver. The stump is passed though a vitallium tube. Two purse string sutures of No. 3 Deknatel silk are inserted on the inferior vena cava around the spot selected for the union. The portal stump and tube are then inserted into the inferior vena cava whose circulation is controlled by means of two rubber covered clamps. Details of the operation are described very well in a paper of Blakemore and Lord.[2]

The principle of the operation having been firmly established modifications of technique and procedure soon followed. It was early recognised that porta-caval shunt operations were not satisfactory. In a number of patients it was impossible to isolate the portal vein because of the extreme vascularity in that region. Also Whipple[28] and his co-workers showed in their studies on dogs with the Eck fistula that the only blood that reached the liver in these cases, came through the hepatic artery with consequent ischæmia and hepatic insufficiency. Because of these two considerations it appears that a spleno-renal shunt is to be preferred.

In 1947 Blalock[6] performed a comparable series of end-to-end spleno-renal anastomosis in dogs using his suture method on the one hand and the vitallium tube method on the other. He found an incidence of thrombosis of 27 per cent in the suture group and 73 per cent in the non-suture group. This suggests that the suture method is superior. The absence of any foreign body and the minimal interference with the vasa-vasorum in the suture technique may be responsible for the better results.

With the use of the suture technique it became clear that there was no need to sacrifice the kidney when a spleno-renal anastomosis was undertaken. The operation of choice therefore seems to be a splenec-